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TREATMENT OF SEVERE DIABETIC ACIDOSIS

A COMPARISON OF METHODS, WITH PARTICULAR REFERENCE TO THE USE OF RACEMIC SODIUM LACTATE

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ST. LOUIS

The method of treating severe diabetic intoxication which is used at present in the St. Louis Children's Hospital may be recommended for the following reasons: (1) It provides a rapid, yet safe, method of restoring the normal acid-base balance of the blood in its broadest sense; (2) it leads to rapid abolition of ketosis, hyperglycemia and glycosuria, and (3) it can be carried out as a simple routine by a standardized procedure, requiring usually but from thirty to sixty minutes and little or no assistance from the laboratory (with the possible exception of an occasional determination of carbon dioxide content necessary for establishing with certainty the diagnosis of diabetic acidosis).

The essentials of the treatment are the immediate administration of insulin, repeated in six hours, and the immediate parenteral administration of adequate amounts of rapidly available alkali in the form of isotonic racemic sodium lactate and of electrolyte in the form of hypotonic Ringer's solution. Both the principles and details of the method have gradually evolved during the past twelve years, largely as a result of studies made in the wards and in the laboratory, not only on diabetic acidosis but on other types of change in the acid-base balance in the body which have a bearing on the problem of diabetes.

Chiefly for the purpose of presenting the data the eighty-six patients who constituted the total series will be divided into three groups: Group 1 comprises patients treated with insulin, together with dextrose and Ringer's solution, but without alkali; group 2, patients treated similarly, but also with administration of sodium bicarbonate at the beginning of treatment, and group 3, patients similarly treated, except that racemic sodium lactate was substituted for sodium bicarbonate. This division happens also to be somewhat chronologically descriptive of the experience. When insulin became available, late in 1922, the first few patients were treated effi-

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ciently [1] by a combination of insulin, sodium bicarbonate and dextrose. Then, for about five years my co-workers and I were misled into believing that alkali had no place in the treatment. Later we reverted to its use in the form of sodium bicarbonate, and for the past four years we have used sodium lactate and have gradually developed our present method of treatment.

RESULTS

Of the eighty-six patients treated during the past twelve years,[1a] the youngest was an infant 8 months of age, and the oldest, a child aged 15 years. Two patients were under 1 year, and three, under 2 years. There were seven deaths, or a mortality rate of 8 per cent. If the mortality rates for the three groups (table 1) are compared, it becomes apparent that they are almost identical. An analysis of the causes of the deaths is, however, enlightening. Of the four deaths in group 1, treated without alkali, one was due to pneumonia, the acidosis being mild and presumably of little importance; the remaining three occurred between twelve and twenty-four hours after institution of treatment, before the acidosis was relieved. In two of these patients the initial carbon dioxide contents of the serum were low (10.6 and 11.6 volumes per cent, respectively). In the third, a value of 28 volumes per cent was found, but in this instance there is some doubt as to the accuracy of the finding, as it was not checked and immediately after the determination had been made a small leak was found in the apparatus used to measure the volumetric content of the gas. The clinical symptoms in this case suggested much more severe acidosis. In all three instances little or no clinical or laboratory evidence of improvement of the acidosis followed institution of treatment, and death resulted from gradual respiratory and cardiac failure; in two instances it occurred about twelve hours, and in the other, about twenty-four hours after institution of treatment. Postmortem examination was permitted in two of these three cases: In one, that of a girl aged 15, whose initial carbon dioxide content was 28 (?) volumes per cent, no pathologic findings were noted other than cloudy swelling and degeneration of the renal tubules, fatty infiltration of the liver and myocardium, some hemorrhagic areas on the epicardium and congestion of the brain with some small surface hemorrhagic areas near the central

1. Hartmann, A. F.: Diabetes Mellitus in Infants and Children, M. Clin. North America **9**:69 (July) 1925.

1a. Since this paper was submitted for publication, five more cases have been encountered, making a total of ninety-one. These additional cases, in all of which recovery occurred, included those of an infant of 11 months with an initial carbon dioxde content of 9.6 volumes per cent, of an infant of 22 months with a carbon dioxide content of 11.5 volumes per cent and of three older children with initial carbon dioxide contents of 12.2, 21.7 and 26 volumes per cent respectively. All were treated by the sodium lactate method, and rapid recovery (as defined on page 10) occurred. With these additional cases the mortality in the group of patients treated with sodium lactate has been reduced to 5.7 per cent.

TABLE 1.—*Results of Treatment in Eighty-Six Cases of Diabetic Acidosis*

Degree of Acidosis, Carbon Dioxide Content of Serum, Vol. %	Total Number of Cases	Type of Treatment: Insulin + Ringer's Solution and Solution of Dextrose; no Alkali					Sodium Bicarbonate + Insulin, Ringer's Solution and Solution of Dextrose					Sodium Lactate + Insulin and Ringer's Solution				
		Number of Cases	Recovery			Number of Deaths	Number of Cases	Recovery			Number of Deaths	Number of Cases	Recovery			Number of Deaths
			Rapid	Slow	Unchecked			Rapid	Slow	Unchecked			Rapid	Slow	Unchecked	
Mild (35-45)	14	12	8	2	2	1*	0	..	..	..	..	2	2	0	0	0
Moderately severe (25-35)	19	12	2	7	3	1†	0	..	..	..	..	7	7	0	0	0
Severe (15-25)	29	14	2	7	5	0	6	6	0	0	0	9	9	0	0	0
Extreme (15 or under)	24	8	2	6	0	2‡	4	4	0	0	1‡	12	12	0	0	2§
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total number of cases	86	46	14	22	10	4	10	10	0	0	1	30	30	0	0	2

* Death due to pneumonia; acidosis relatively unimportant.

† Death in 2 cases apparently due entirely to effects of acidosis, which was unrelieved.

‡ Death due to pneumonia; acidosis relieved before death.

§ Death in 1 case due to pneumonia, and in another, to hyperthermia; acidosis relieved in each instance.

TABLE 2.—*Data on Patients with Diabetic Acidosis Before Treatment (Group 1) and Results of Chemical Determinations on Blood Serum* *

Case	Sex	Date	Age, Years	Weight, Kg.	Carbon Dioxide Content, Vol. %	p_H	Sodium Chloride, Mg. per 100 Cc.	Proteins, per Cent	Inorganic Phosphorus, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Total Base, Millimols	BR,† Millimols	Dextrose, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Outcome
1	M	2/14/24	6½	14.5	10.6	....	...	.....	...	....	...	....	237	32.0	Died
2	F	8/24/26	12	28.0	15.0	7.10	...	.....	...	....	...	....	470	....	Recovered
3	M	9/16/26	8	20.0	11.0	7.00	497	9.99 (R)	5.6	22.4	119	7.0	488	37.8	Recovered
4	F	1/26/27	14	50.0	13.8	(7.10)	579	9.99 (R)	5.8	(18.0)	147	17.0	457	36.8	Recovered
5	F	2/11/25	12	35.0	18.4	6.97	579	.....	...	....	...	....	475	30.8	Recovered
6	F	3/31/24	13	37.0	13.4	....	...	.....	...	....	...	....	480	43.6	Recovered
7	F	2/ 1/27	12	25.0	25.0	....	...	6.98 (R)	...	....	...	....	396	....	Recovered
8	M	6/ 3/26	10	25.0	14.6	7.17	538	9.99 (R)	(5.6)	(18.0)	128	6.0	516	52.2	Recovered
9	F	4/ [illegible]/27	7	20.0	23.5	7.25	562	8.28 (R)	...	13.9	...	....	210	26.0	Recovered
10	M	1/29/[illegible]	6	14.0	22.0	....	...	.....	...	....	...	....	318	....	Recovered
11	M	10/29/23	12½	25.0	19.9	....	...	.....	...	27.9	...	....	292	48.2	Recovered
12	F	9/25/25	12	20.0	19.6	....	579	.....	...	....	...	....	290	29.0	Recovered
13	M	12/ 5/27	13	40.0	20.3	....	527	10.41 (R)	...	33.1	...	....	479	35.0	Recovered
14	M	5/26/28	15	45.7	25.3	7.10	544	8.23 (K)	(5.6)	15.1	150	27.0	492	36.6	Recovered
15	M	1/17/25	2⅛	9.9	20.7	....	538	.....	...	....	...	....	305	46.6	Recovered
16	F	2/13/25	12	35.0	19.8	....	...	.....	...	....	...	....	332	23.4	Recovered
17	F	1/25/27	14	50.0	12.7	....	565	9.13 (R)	...	....	...	....	386	29.6	Recovered
18	F	8/ 4/26	13	40.0	18.0	....	...	.....	...	....	...	....	389	44.0	Recovered

* (R) indicates determination by refractometer, and (K) determination by micro-Kjeldahl procedure. The figures in parentheses are assumed values necessary for calculation of BR.

† The figures in this column indicate the salts of residual acids (R) left after the determination of the specific ones indicated (Cl, HCO_3, protein, phosphate and lactate).

gyrus. The postmortem examination in the other case, that of a 7 year old boy, whose initial carbon dioxide content was 10.6 volumes per cent (case 1, table 2, chart 1), revealed mural thrombi in both ventricles and evidence of fresh bronchopneumonia in addition to tonsillitis, otitis media and stomatitis. There was also fatty degeneration of the heart, kidneys and liver. Glycogen stains of the liver, however, showed that the glycogen content was markedly increased. In the instance in which postmortem examination was not permitted the diabetic acidosis seemed uncomplicated and appeared to be the direct cause of death.

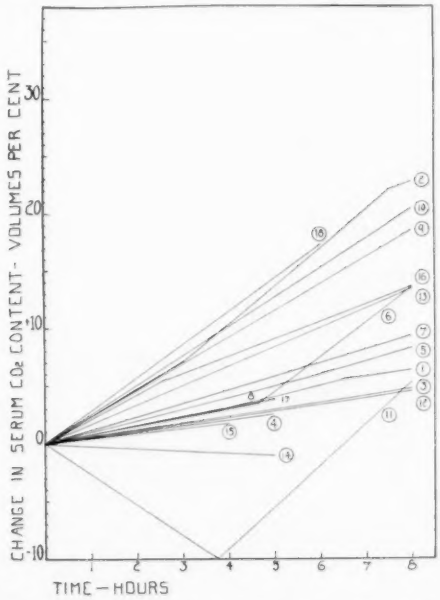

Chart 1.—Curves showing rate of recovery from diabetic acidosis when the treatment consisted of insulin, water, Ringer's solution and dextrose solution, but no alkali. The doses of insulin per kilogram of body weight were as follows: case 1, 5.5 units; case 2, 3.6 units; case 3, 3 units; case 4, 3 units; case 5, 2.9 units; case 6, 2.8 units; case 7, 2.4 units; case 8, 1.8 units; case 9, 1.5 units; case 10, 1.5 units; case 11, 1.1 units; case 12, 1.3 units; case 13, 1.3 units; case 14, 1.1 units; case 15, 1 unit; case 16, 1 unit; case 17, 1 unit, and case 18, 0.9 unit. The average dose was 2 units per kilogram of body weight.

The single death in group 2, treated with sodium bicarbonate (case 1, table 3, chart 2), occurred about seventeen hours after the patient's admission. The carbon dioxide content had increased from 7.8 to 48 volumes per cent, and ketosis had disappeared, but circulatory failure with marked oliguria persisted. The temperature on admission was 104.5 F.; it rose to 106.5 F. before death. A few fine râles were heard

TABLE 3.—*Data on Patients with Diabetic Acidosis Before Treatment (Group 2) and Results of Chemical Determinations on Blood Serum*

Case	Sex	Date	Age, Years	Weight, Kg.	Carbon Dioxide Content, Vol. %	*pH*	Sodium Chloride, Mg. per 100 Cc.	Proteins, per Cent	Inorganic Phosphorus, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Total Base, Millimols	BR, Millimols	Dextrose, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Outcome
1	M	4/ 3/28	9	24.0	18.7	7.00	515	7.88 (K)	8.5	44.1	147	28.0	709	48.0	Recovered
2	M	6/ 6/28	9	23.0	6.9	6.95	473	6.80 (K)	(6.0)	(18.0)	141	41.1	922	60.0	Recovered
3	F	1/31/27	12	25.0	15.0	7.10	562	9.56 (R)	4.6	(18.0)	133	8.8	413	33.0	Recovered
4	M	4/11/23	7	20.0	7.8	....	...	.....	...	51.7	...	....	402	61.0	Recovered
5	M	4/ 7/23	11	25.0	15.7	....	...	.....	...	....	...	....	672	....	Recovered
6	M	9/16/27	3	12.7	16.8	....	...	.....	...	....	...	....	234	....	Recovered
7	F	10/ 8/23	13	30.0	10.6	....	...	.....	...	....	...	....	712	76.5	Recovered
8	M	4/11/23	7	20.0	19.0	....	...	.....	...	....	...	....	293	....	Died

* (K) indicates determination by micro-Kjeldahl procedure, and (R) determination by refractometer. The figures in parentheses indicate assumed values necessary for calculation of BR.

in the chest, but no areas of consolidation were detected; however, since a definite chill preceded the rise in temperature, after which apparently the acidosis became much worse, it is possible that the child had pneumonia without physical signs. Autopsy was not permitted.

Of the two deaths in group 3, treated with sodium lactate, one (case 1, table 4, chart 3) occurred about five hours after institution of treatment and was apparently due to hyperpyrexia, the temperature, which was 101 F. on admission, rising rapidly to over 108 F. (42.5 C.). In this instance the carbon dioxide content had risen from 8.5 to 36.8 volumes per cent, and hyperpnea had disappeared. The cause of the

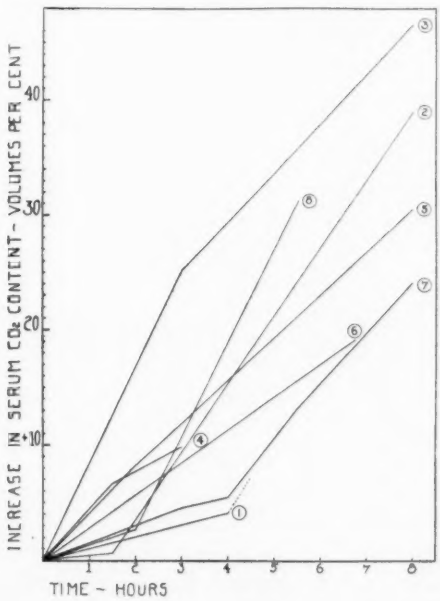

Chart 2.—Curves showing rate of recovery from diabetic acidosis when the treatment consisted of administration of solution of sodium bicarbonate plus insulin, water, dextrose, and Ringer's solution. The doses of molar sodium bicarbonate and insulin per kilogram of body weight were as follows: case 1, 12 cc. of sodium bicarbonate and 3.3 units of insulin; case 2, 6.5 cc. of sodium bicarbonate and 3.7 units of insulin; case 3, 6 cc. of sodium bicarbonate and 2.4 units of insulin; case 4, 6 cc. of sodium bicarbonate and 4.5 units of insulin; case 5, 4.8 cc. of sodium bicarbonate and 2.9 units of insulin; case 6, 4.6 cc. of sodium bicarbonate and 3.1 units of insulin; case 7, 3.2 cc. of sodium bicarbonate and 6.3 units of insulin; case 8, 3 cc. of sodium bicarbonate and 1.8 units of insulin. The average doses per kilogram of body weight were 5.8 cc. for sodium bicarbonate and 3.5 units for insulin.

TABLE 4.—*Data on Patients with Diabetic Acidosis Before Treatment (Group 3) and Results of Chemical Determinations on Blood Serum*

Case	Sex	Date	Age, Years	Weight, Kg.	Carbon Dioxide Content, Vol. %	p_H	Sodium Chloride, Mg. per 100 Cc.	Proteins, per Cent	Inorganic Phosphorus, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Total Base, Millimols	BR, Millimols	Dextrose, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Outcome
1	F	12/20/30	11	35.0	8.5	...	600	10.5 (K)	5.7	....	...	....	537	47.0	Died
2	F	7/14/31	6	15.±	10.8	...	...	.....	...	....	...	....	560	....	Died
3	M	5/30/33	21	44.0	14.4	...	562	10.7 (K)	...	....	...	....	588	49.0	Recovered
4	F	6/12/33	11 mos.	7.3	15.0	...	...	.....	...	....	...	....	300	....	Recovered
5	F	2/23/33	8 mos.	6.4	12.8	...	606	9.02 (K)	4.7	32.2	...	....	628	50.0	Recovered
6	F	10/ 6/33	2⅓	11.3	10.4	...	596	8.72 (K)	...	32.8	...	....	525	37.5	Recovered
7	F	7/ 7/30	3	9.6	20.3	...	521	.....	...	26.4	...	....	508	....	Recovered
8	M	5/12/32	10	27.0	11.4	...	595	6.70 (K)	...	....	...	....	360	32.0	Recovered
9	F	4/ 4/32	13	45.0	17.0	...	573	8.85 (K)	4.5	22.1	...	....	420	30.0	Recovered
10	M	12/20/32	6	17.7	15.1	...	579	8.99 (K)	...	30.2	...	....	500	31.0	Recovered
11	M	5/ 1/31	12	30.0	16.1	(7.1)	603	8.58 (K)	3.9	64.3	143	8.4	508	27.0	Recovered
12	M	1/28/31	10	25.0	14.4	...	503	8.41 (K)	...	....	...	....	655	53.5	Recovered
13	M	7/26/32	4½	14.5	16.2	...	608	6.96 (K)	...	23.9	...	....	437	37.0	Recovered
14	F	2/29/32	9	21.9	13.6	7.0	544	7.60 (K)	4.2	32.0	...	....	...	33.0	Recovered
15	M	8/21/31	12	30.0	15.0	...	...	.....	...	....	...	....	316	....	Recovered
16	F	12/18/30	12	35.4	24.8	...	...	.....	...	25.2	...	....	315	....	Recovered

* (K) indicates determination by micro-Kjeldahl procedure. The figures in parentheses indicate assumed values necessary for calculation of BR.

hyperpyrexia was not determined with certainty, permission for autopsy being refused, but the condition may have been due in part to the method of administration of the lactate solution and will be discussed later. In the other case (case 2, table 4, chart 3) death occurred about four hours after onset of treatment, the temperature rising from 104 F. to 108 F. The history and physical findings indicated the presence of pneumonia. Autopsy was not permitted. During the brief period of treatment, the carbon dioxide content had risen from 10.8 to 47 volumes per cent.

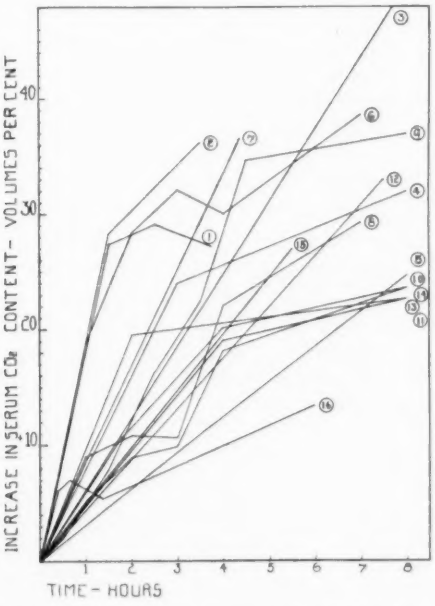

Chart 3.—Curves showing rate of recovery from diabetic acidosis when the treatment consisted of sodium lactate plus insulin, water and Ringer's solution. The doses of molar racemic sodium lactate and insulin per kilogram of body weight were as follows: Case 1, 18.5 cc. of sodium lactate and 2.9 units of insulin; case 2, 13.3 cc. of sodium lactate and 5 units of insulin; case 3, 13.2 cc. of sodium lactate and 2.4 units of insulin; case 4, 13 cc. of sodium lactate and 3.6 units of insulin; case 5, 12.5 cc. of sodium lactate and 2.8 units of insulin; case 6, 12.5 cc. of sodium lactate and 2.6 units of insulin; case 7, 11.5 cc. of sodium lactate and 4.2 units of insulin; case 8, 11.1 cc. of sodium lactate and 2.5 units of insulin; case 9, 10 cc. of sodium lactate and 2.5 units of insulin; case 10, 9.6 cc. of sodium lactate and 2.8 units of insulin; case 11, 8.3 cc. of sodium lactate and 3 units of insulin; case 12, 8 cc. of sodium lactate and 2.4 units of insulin; case 13, 6.9 cc. of sodium lactate and 2.5 units of insulin; case 14, 6.8 cc. of sodium lactate and 3.9 units of insulin; case 15, 6.4 cc. of sodium lactate and 1.2 units of insulin; case 16, 3.8 cc. of sodium lactate and 2.9 units of insulin. The average doses per kilogram of body weight were 10.3 cc. for sodium lactate and 3 units for insulin.

venously at the beginning of treatment varied from 12 cc. of a molar solution per kilogram to 3 cc., the average dose being 5.8 cc. The cases are numbered in accordance with the size of the dose of sodium bicarbonate, the patient in case 1 receiving the largest dose and the patient in case 18, the smallest. It can be seen from charts 2 and 4 that recovery in this group was much more rapid than in the group treated without alkali. What was still more striking than the effect on the carbon dioxide content of the serum was the effect noted clinically, the patients in this group showing a much more rapid rate of recovery from hyperpnea and tachycardia. It is also apparent from a study of chart 2 that the speed of recovery during the first two hours is more directly proportional to the dose of bicarbonate than to the dose of insulin. The exception (case 1) is worthy of special comment. The protocol of this case and detailed data incident to the patient's recovery have been published previously.[2] After administration of insulin, dextrose, Ringer's solution and solution of sodium bicarbonate, the patient remained in a state of shock; the pulse was poor and marked cyanosis persisted. Despite the administration of sodium bicarbonate little immediate increase in the carbon dioxide content of the plasma resulted; instead, great increase in both lactic acid and diacetic acid occurred. Consequently, when improvement of the circulation took place, alkalosis resulted after complete abolition of ketosis. No completely satisfactory explanation of the unusual response has been found at the present time. No clinical symptoms accompanied the development of alkalosis, and recovery was otherwise uneventful. From chart 4 it may be seen that the average result of treatment with sodium bicarbonate is to increase the carbon dioxide content slightly more than 3 volumes per cent per hour for the first four hours. After eight hours the average increase is 35 volumes per cent.

Patients Treated with Sodium Lactate (Group 3).—In this group of 16 cases the dose of sodium lactate given initially varied from 3.8 to 18.5 cc. of a molar solution per kilogram, the average dose being 10.3 cc. As in the previous groups, the cases are numbered in accordance with the size of the dose of sodium lactate, the patient in case 1 receiving the largest dose. The amount of insulin given during the first six hours varied from 1.2 to 5 units per kilogram, the average amount being 3 units. From charts 3 and 4 it may be seen that for the group as a whole recovery was more rapid than in either of the other two groups. Again

2. Hartmann, A. F., and Darrow, D. C.: Chemical Changes Occurring in the Body as the Result of Certain Diseases: III. The Composition of the Plasma in Severe Diabetic Acidosis and the Changes Taking Place During Recovery, J. Clin. Investigation **6**:257 (Oct.) 1928, case 1.

there is a more direct relationship between the speed of recovery during the first one or two hours and the size of the dose of sodium lactate. The most notable exception is case 5, and it proved to be an exception for the following reasons: The patient, the youngest in the series, was 8 months of age and was admitted late in the afternoon with the symptoms of severe acidosis associated with pharyngitis, otitis media and pneumonia. The previous history did not suggest the presence of diabetes, and after a sample of blood was obtained for chemical analysis the routine treatment for severe nondiabetic acidosis was ordered. To this end

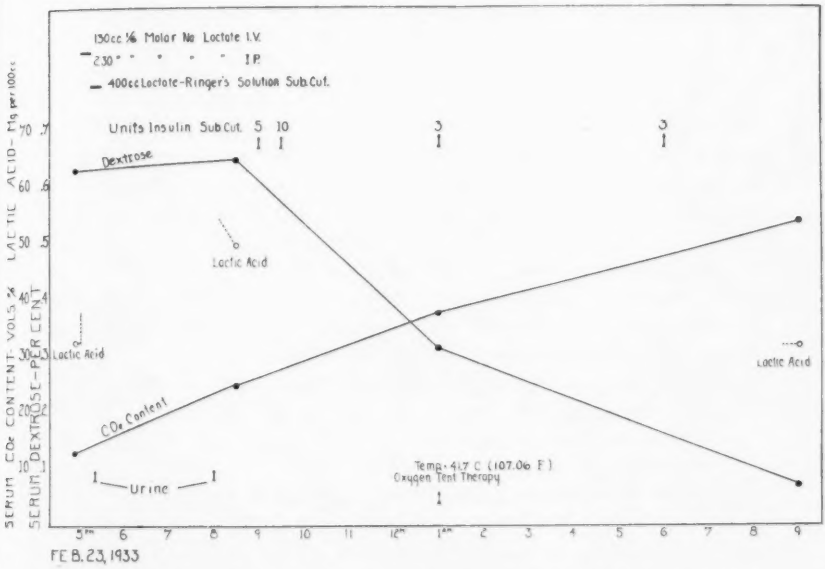

Chart 5.—Curve showing the results of treatment in a case of severe acidosis not immediately recognized as diabetic. The patient was aged 8 months and weighed 6.6 Kg. The immediate treatment consisted of racemic sodium lactate plus lactate-Ringer's solution. Insulin was given later. Pneumonia and otitis media complicated the acidosis.

60 cc. of sixth-molar sodium lactate per kilogram of body weight was given parenterally. During the next four hours the patient showed improvement clinically, and the carbon dioxide content rose from 12.8 to 24.5 volumes per cent (chart 5). At this time, the urine was found to contain sugar, as well as diacetic acid, and the sugar content of the blood was found to be 645 mg. per hundred cubic centimeters. The filtrate made from the initial specimen of blood, which had been set aside in the icebox, was also examined, and the sugar content was found to

be 628 mg. per hundred cubic centimeters. This information made it obvious that diabetic acidosis was present, and insulin was administered in the usual dose of 2 units per kilogram of body weight; after this recovery continued at an accelerated rate. The four hour delay before administration of insulin is, of course, the explanation for the slower recovery in this case. Subsequently this child recovered from pneumonia; later a mastoidectomy had to be performed because of the otitis media. At the time of writing the patient is a healthy-looking infant. This case, of course, demonstrates that metabolism of sodium lactate with formation of sodium bicarbonate takes place in the diabetic state in the absence of insulin administration, a fact which has been previously noted and commented on.[3]

The average result in these sixteen cases (chart 4) is such as to indicate that almost as much is accomplished during the first hour of treatment with sodium lactate as is accomplished in eight hours when no alkali of any sort is given. The slope of the curve for increase in alkali reserve also differs, being steepest early during the course of treatment, and gradually tapering off as a normal carbon dioxide content is reached. The average gain in carbon dioxide content during the first eight hours was 30 volumes per cent. As in the group treated with sodium bicarbonate, the clinical appearance of improvement tended to coincide with the rise in carbon dioxide content, particularly in regard to dyspnea and tachycardia and to turgor and color of the skin.

Despite the fact that abnormally high initial levels of lactate were present in the blood in a number of cases, in all instances in which it was determined, the concentration of blood lactate had returned to a normal level in from two to four hours after injection of the sodium lactate. In five instances (cases 10, 13 and 14, table 4, chart 3, and two cases observed in 1934) the excretion of lactic acid in the urine was calculated, and it was found that the losses varied from 6.6 to 11.5 per cent of the total amount injected and that the average amount lost through urinary excretion was 8.3 per cent.

In addition to its effect of increasing the alkali reserve, the large amounts of isotonic solution of sodium lactate do, of course, tend to relieve dehydration (as indicated by skin turgor and body weight) and anhydremia (as indicated by a fall in the protein concentration and a rise in the water content of the serum). The administration of Ringer's solution (or lactate-Ringer's solution) in an amount equivalent to 40 cc. per kilogram of body weight immediately after the administration of sodium lactate aids further in relieving dehydration and

3. Hartmann, A. F., and Darrow, D. C.: J. Clin. Investigation **6**:257 (Oct.) 1928.

at the same time restores lost electrolytes (sodium, potassium, calcium, magnesium and chloride ions). Consequently, with the complete abolition of ketosis,[4] which usually occurs between six and eighteen hours after treatment is instituted, recovery of the acid-base balance of the blood in its broadest sense tends to be completed during the first twelve hours of treatment, entirely without dependence on absorption from the gastro-intestinal tract and with but a minimal amount of assistance from renal activity.

The curves for the amount of sugar in the blood in the individual cases and the curve for the average amount of the group are shown in chart 6. In this group of cases, as a rule, 2 units of insulin per kilo-

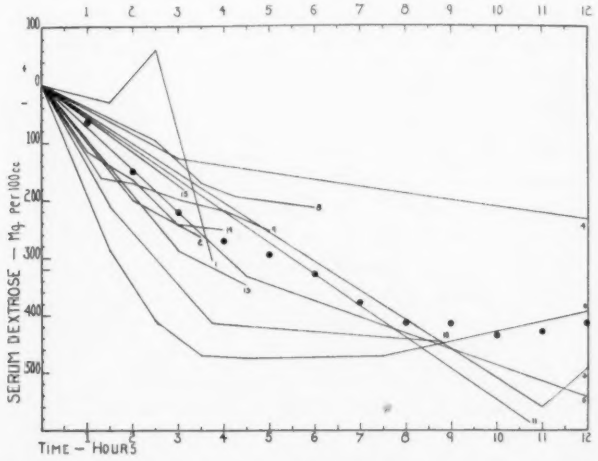

Chart 6.—Curves showing the values for serum dextrose in the group of patients treated with sodium lactate. The average values are shown in large dots.

4. In addition to the testing for diacetic acid in the urine by addition of ferric chloride, a number of other checks on the state of ketosis were usually made. Whenever protein-free filtrates of the serum were prepared for the determination of lactic acid, preliminary distillation of the acidified filtrates was made, the acetone preformed and that resulting from the decomposition of aceto-acetic acid being caught either in Scott-Wilson reagent as a qualitative test for acetone or in alkaline iodine solution for quantitative estimation. When determinations of total base content were made in addition to determinations of the most important normally occurring acids (chloride, bicarbonate, protein, phosphate and lactate), the remaining acid, of course, served as an additional check on the concentration of the ketone acids. In a few instances, when cooperation could be obtained, expired air was blown through the Scott-Wilson reagent to check for the presence of acetone in the alveolar air.

gram of body weight (one half of the dose being administered intravenously and one half, subcutaneously) were given at the start, and from four to six hours later another unit per kilogram was given subcutaneously. In two instances (cases 3 and 6) hypoglycemia (without clinical symptoms) occurred between eight and twelve hours after the onset of treatment. For this reason, in the method of treatment used at present the second dose of insulin is reduced to one-half unit per kilogram and is given six hours after the initial dose.

COMMENT

In a recent paper on the pathogenesis and prognosis of diabetic coma, Bertram [5] in reviewing the literature from 1922 to 1932 included the figures given for mortality rates in twenty-five different series of cases. The figures varied between 5.6 and 73.9 per cent, the average rate for the twenty-five series reviewed being 29.1 per cent. The mortality rate of 8 per cent in the entire series of eighty-six cases described in this article compares favorably with these figures, the results being excelled only in Petrén's series.[6] As Bertram pointed out, however, such variation in mortality rates is due not only to differences in methods of treatment but also to differences in material, particularly as regards severity of acidosis and of complications. These points should also be borne in mind in considering the extremely low mortality rate among the children and adolescent patients who formed the basis of Joslin's study recently reported by White.[7] Only one death occurred in seventy cases. In view of such a low mortality rate it is no wonder that Joslin and his co-workers believed that no improvement need be sought for their method of treatment, which excludes alkali with the exception of that derived from fruit juices taken by mouth. It should be remembered, however, that of forty-six of the patients in this series treated in essentially the same manner as that advocated by Joslin and his co-workers four died and that in many of the fatal cases recorded in the literature the patients had been similarly treated. The exceptionally low mortality rate in Joslin's series may have been due to the fact that a relatively smaller percentage of his patients had serious complicating infections and that circulatory and respiratory collapse were not present or imminent at the time the patients were admitted to the hospital. His data certainly indicate that severe acidosis was present in a fairly high percentage of his

5. Bertram, F.: Pathogenese und Prognose des Coma Diabeticum, Ergebn. d. inn. Med. u. Kinderh. **43**:258, 1932.

6. Petrén, K.: Ueber die Gründe der diätetischen Behandlung des Diabetes, besonders des Diabetes Gravis, München. med. Wchnschr. **74**:1123, 1927.

7. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932.

patients.[8] That a number of his patients, however, recovered slowly and still had marked acidosis on the second and third days of treatment is apparent from his tabulated data. The question naturally is raised whether or not the children in Joslin's series might not have been still better off had they been relieved of their acidosis more speedily, and whether or not some of his adult patients who died might not have been saved by the judicious use of alkali. In this regard it is apparent from some of his comments[9] that Joslin has less fear of sustained severe acidosis than of the possibility that alkalosis might develop. I cannot but disagree with such a point of view for a number of reasons: 1. There is abundant experimental and clinical evidence to the effect that death may occur directly from the effects of acid intoxication. As early as 1877, von Walters[10] studied the effect of administration of hydrochloric acid to animals and demonstrated that death occurred when approximately enough acid was administered to neutralize all of the alkaline reserve of the body fluids. In the same studies he also proved that alkali has a life-saving value if given promptly enough. Subsequent experimental work confirmed von Walters' results. In clinical experience in the past it has been a common occurrence to see infants succumb rapidly to the effects of acidosis and dehydration resulting from diarrhea and to find no evidence at autopsy to explain such deaths. On the other hand, it is now taken for granted that measures relieving acidosis and dehydration may either prevent or postpone deaths in such cases. That some tolerance to acidosis may be acquired is readily admitted, particularly when the acidosis is slow to develop, as it often is when it is associated with progressive renal lesions. 2. While severe alkalosis is unquestionably dangerous and may also be fatal, the danger of mild or moderate degrees of alkalosis is overrated, and measures for both prevention and relief are simple and effective.[11] Joslin's own experience

8. For the group of children reported on by White,[7] a number of extremely low figures, values from 3 to 5 volumes per cent, for the carbon dioxide-combining power of the plasma are given. Joslin also mentioned the case of one adult patient who walked into the hospital with a carbon dioxide-combining power of 2 volumes per cent! The accuracy of such values, however, has to be questioned when one considers that expired alveolar air with which plasma is equilibrated contains carbon dioxide in amounts of about 3 volumes per cent and that after equilibration with such alveolar air the carbon dioxide tension in the plasma should be increased over what it was; moreover, when increased acidity occurs combination of carbonic acid with base liberated from the protein buffers should result.

9. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928.

10. von Walters, F.: Untersuchungen über die Wirkung der Säuren auf den thierischen Organismus, Arch. f. exper. Path. u. Pharmakol. **7**:148 (Aug.) 1877.

11. Hartmann, A. F.: Acidosis, Alkalosis and Ketosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. I, sect. 2, chap. 1.

with the development of alkalosis in diabetic patients hardly justifies his stand, it seems. His fear of alkali seems to be based chiefly on two cases: In one mild alkalosis developed after treatment without alkali and the patient died about ten days later of cerebral hemorrhages; in the other the patient had been treated in another clinic with an unnecessarily large dose of sodium bicarbonate plus insulin. This patient apparently made a rapid and uneventful recovery from severe acidosis, despite the fact that alkalosis developed subsequently. Treatment of the latter patient with hydrochloric acid was instituted because of the fear of symptoms. It seems that this case might even better have been used as an example of the harmlessness of accidental alkalosis following administration of too much alkali.

The essential point, however, concerning the use of alkali is that advantage may be taken of its effect in hastening recovery from acidosis without fear that dangerous degrees of alkalosis might develop if the proper precautions are taken. The chief factors tending toward the production of alkalosis after administration of alkali plus insulin are: (1) excessive doses of alkali, (2) a reduction in the chloride concentration of the body fluids, (3) the development of edema and oliguria resulting from diminished plasma proteins and (4) the presence of actual renal insufficiency, which may curtail the excretion of excess alkali.

Dosage of Alkali.—If sodium bicarbonate itself is given intravenously, the dose should not exceed 0.5 Gm. per kilogram of body weight, which is sufficient, as a rule, to increase the carbon dioxide content of the plasma by about 15 volumes per cent. If much more is given there is danger of development of alkalosis of either or both of two types: (1) a type due to actual excess of alkali, particularly if oxidation of the ketone acids with liberation of base is occurring at a rapid rate in response to insulin, and (2) a type of alkalosis caused by a deficit of carbon dioxide in the presence of a normal, high or slightly low bicarbonate content. The latter condition tends to develop because in the presence of compensatory hyperpnea during the period of acidosis the tension of carbonic acid is reduced and the intravenous administration of sodium bicarbonate in large amounts may increase the ratio of the bicarbonate to the carbonic acid too rapidly, even though the normal amount of bicarbonate is not exceeded. If sodium lactate is given, approximately the equivalent of 1 Gm. of sodium bicarbonate per kilogram may safely be administered. This amounts to about 60 cc. of the sixth-molar solution per kilogram of body weight. The greater safety afforded by medication with sodium lactate is, of course, due to the fact that the sodium lactate has to be metabolized before it is converted into sodium bicarbonate, and such metabolism requires from two to four

hours for completion after the start of administration. It is important, however, to give the racemic sodium lactate in isotonic strength. An increase of from 25 to 50 per cent over the basal rate of oxygen consumption (apparently due to the oxidation of the d-isomer in the racemic mixture) follows the intravenous administration of racemic sodium lactate to normal human subjects [12] when the preparation is given in amounts equivalent to 7 cc. of molar solution per kilogram of body weight. A similar effect probably occurs in the diabetic patient. If the latter is already dehydrated and a hypertonic solution of sodium lactate is given, it is conceivable that such increase in heat production may raise the body temperature to a dangerous level. My co-workers and I believe that this is the explanation for the hyperpyrexia which occurred in one of our fatal cases (case 1, chart 3, table 4). The sodium lactate was given in molar strength to that patient and also to the patient in case 2. Subsequently a sixth-molar (isotonic) solution was used, and no such hyperpyrexia developed.

Rôle of Chloride Concentration.—The tendency on the part of the blood and body fluids to maintain a normal total electrolyte concentration and osmotic pressure, despite variation in the individual anions, is well known. If, after the normal water content has been restored to the blood and body fluids, the chloride level is much reduced (as it tends to be if severe vomiting and dehydration have occurred previously and saline solution has not been administered), base released by oxidation or urinary excretion of organic acid radicals will be retained in the body fluids in combination with the bicarbonate radical. In such situations alkalosis may occur without administration of alkali and, of course, may be intensified as a result of the giving of alkali. If, however, the chloride level is restored to normal by the administration of sodium chloride or Ringer's solution before oxidation of the organic acids is completed, the base released by the oxidation of such acids finds its way into the urine as bicarbonate and the urinary excretion prevents excess of the alkali in the body fluids.

Edema Following Diabetic Acidosis.—The nature of the dietetic management of diabetes before the discovery of insulin was often such that in severe cases a stage of extreme malnutrition was reached. Patients in whom this occurred must frequently have had a reduction of plasma proteins and "nutritional" edema. Two striking examples of edema of this type occurred in this series because of poor control through diet and insulin medication. During periods of severe acidosis, particularly when the acidosis is accompanied by much vomiting and a

12. Hartmann, A. F.: Unpublished data from the Laboratory of the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital.

diminished intake of food, the tendency toward still further reduction of plasma proteins and formation of edema may be entirely masked by the dehydrating effect of the vomiting and the acidosis. On cessation of vomiting and relief from acidosis edema would tend to occur in such cases, particularly if an abundance of fluid containing the sodium ion were given. If conditions were such that an excess of bicarbonate in the body fluids tended to be present the tendency toward edema and oliguria would cause alkalosis to persist, despite administration of sodium chloride. Administration of plasma proteins (citrated whole blood or plasma) or some substitute, such as acacia, would remove such a tendency toward edema and permit the kidney to aid in restoring a normal electrolyte balance in the blood.

Renal Insufficiency.—Aside from the oliguria associated with diminished plasma protein, after severe and prolonged acidosis oliguria or anuria tends to occur because of damage to the kidney. The occurrence of such a renal insufficiency is not confined to patients with diabetes; the condition is frequently seen to follow prolonged states of severe acidosis and dehydration in infants and children suffering from severe diarrhea. The question naturally raised is whether or not such renal damage is not a result of the severe and prolonged acidosis and whether the earliest possible relief from acidosis is not always indicated to prevent such an important complication.

In a recent paper, Kydd [13] commented on the inadequacy of administering merely water and insulin in the treatment of diabetic acidosis and stressed the value of giving sodium chloride. He also recognized the value of sodium bicarbonate in certain cases and expressed the belief that a combination of sodium bicarbonate and sodium chloride should be used. This was the conclusion which a co-worker and I [3] reached several years ago, with the difference that we believed that Ringer's solution was superior to sodium chloride and that administration of dextrose solution also had a place. The advantages of sodium lactate over sodium bicarbonate, which have led us to substitute the one for the other, evidently have not sufficiently impressed Kydd, who erroneously stated that "the solution (sodium lactate) also is not immediately available because it must be given intravenously, and, therefore, cannot be made in advance if non-specific reactions are to be avoided." The ease with which it can be prepared, its stability, its compatibility with other solutions and the facility with which it is tolerated by blood and tissues are, of course, some of the reasons that the use of sodium lactate has been substituted for that of sodium bicarbonate.

13. Kydd, D. M.: Salt and Water in the Treatment of Diabetic Acidosis, J. Clin. Investigation **12**:1169 (Nov.) 1933.

Method of Administering Sodium Lactate.—In regard to the manner in which sodium lactate may be administered, my co-workers and I have made the following observations: (1) When the entire amount is given subcutaneously in isotonic strength, a slight delay of about two hours occurs in the reaching of the peak of increase in the amount of bicarbonate: (2) when a molar solution of racemic sodium lactate is diluted with 5 volumes of Ringer's solution, the resultant solution is apparently sufficiently hypertonic to delay somewhat its absorption from the peritoneal cavity and subcutaneous tissues; (3) when the entire amount of isotonic sodium lactate is given intravenously at a rapid rate, the quickest

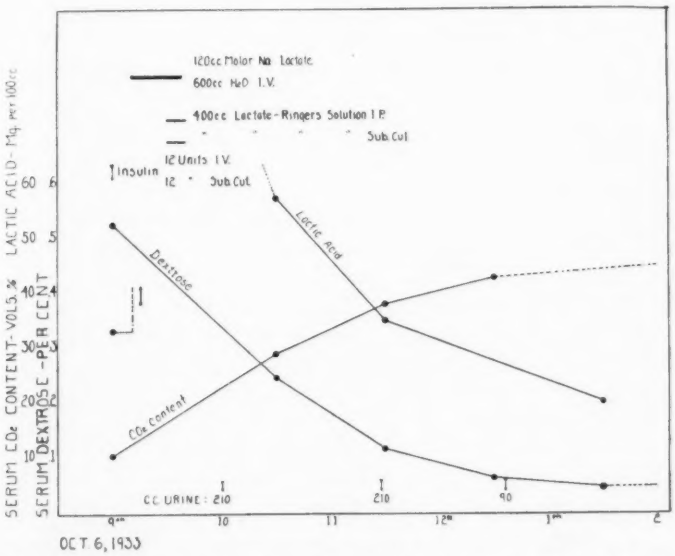

Chart 7.—Curves showing the results of treatment in a patient with severe diabetic acidosis treated by the method which is thought most efficient at the present time, namely, administration of racemic sodium lactate, insulin, and lactate-Ringer's solution. The patient in this case was aged 2⅓ years and weighed 11.3 Kg.

relief of acidosis results (chart 6); when the sodium lactate is given at a much slower rate by the continuous intravenous drip method, a slower but still satisfactorily rapid recovery from acidosis results. Another method will be tried at the next opportunity which may perhaps prove best of all: The entire amount of the isotonic sodium lactate solution (60 cc. per kilogram of body weight) will be mixed with the entire amount of Ringer's solution (40 cc. per kilogram of body weight) and about one half of the resulting mixture will be given intravenously, the

remainder being administered by a combination of the intraperitoneal and subcutaneous routes.[14]

SUMMARY AND CONCLUSIONS

As a result of a critical study on eighty-six patients with diabetic acidosis treated at the St. Louis Children's Hospital during the past twelve years, my co-workers and I have come to the conclusion that the most effective method of treatment demands the use of alkali (sodium bicarbonate or racemic sodium lactate), together with insulin, Ringer's solution and solution of dextrose. When sodium lactate is used instead of sodium bicarbonate, the dextrose solution may be omitted. The method of treatment of severe diabetic acidosis which is recommended at the present time (chart 7) includes:

1. Immediate parenteral administration (one half intravenously, the remainder subcutaneously and intraperitoneally) of 60 cc. of a sixth-molar solution of racemic sodium lactate [15] per kilogram of body weight.

2. Immediate administration of 2 units of insulin per kilogram of body weight.

3. Administration of 40 cc. of Ringer's solution per kilogram of body weight as soon after the administration of sodium lactate as possible.

4. Repeated administration of insulin six hours later in a dose of one-half unit per kilogram of body weight.

5. Transfusion of citrated whole blood or plasma (20 cc. per kilogram of body weight) if edema due to reduced plasma protein develops.

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14. In two of the five cases encountered since this paper was submitted for publication, this method was used. Apparently a more rapid absorption of the fluid occurred from both the peritoneal cavity and the subcutaneous tissues. A slightly more rapid recovery of the carbon dioxide contents also resulted. Thus, in the last case to be seen, that of an infant of 22 months, weighing 10 Kg., with an initial carbon dioxide content of 11.5 volumes per cent, 600 cc. of one-sixth molar sodium lactate was added to 400 cc. of Ringer's solution; 300 cc. of the mixture was given intravenously and 350 cc. each by the intraperitoneal and subcutaneous routes. Samples of blood were taken at hourly intervals after the administration of fluid was completed. The following carbon dioxide contents were noted: at the first determination, 25; at the second, 34; at the third, 40; at the fourth, 47 volumes per cent, respectively.

15. The racemic sodium lactate used was in sterile 40 cc. ampules of molar strength.

DIFFERENTIAL DIAGNOSIS BETWEEN CEREBRAL HEMORRHAGE AND CEREBRAL THROMBOSIS

A CLINICAL AND PATHOLOGIC STUDY OF 245 CASES

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The purpose of this study is to present an analysis of 245 cases of lesions of the cerebral vessels in which the diagnosis was proved at necropsy in order to determine the significant findings in the history and examination that will aid in the differential diagnosis between cerebral hemorrhage and cerebral thrombosis.

The average physician rarely attempts to differentiate between these types, and the majority of cases of cerebral vascular lesion are indiscriminately labelled "cerebral hemorrhage." This is true despite the difference in the symptoms, the signs and especially the prognosis of these conditions. Also, with the more recent application of surgical treatment [1] toward the relief of cerebral hemorrhage, it is evident that the treatment becomes even more divergent than that previously advocated. The academic exercise of localizing the lesion, which is so intriguing to the neurologist and internist, must be supplemented by an ability to differentiate the types of lesion. Treatment or the possible alleviation of any cerebral lesion demands accurate knowledge of the nature and location of that lesion. It seems, therefore, that the hope of occasionally relieving the previously almost totally fatal cerebral hemorrhage will force the members of the medical profession to learn not only to localize but to determine more accurately the nature of the process in patients with cerebral vascular lesions. The need of a series of proved cases of cerebral vascular lesions is indisputable and has been repeatedly noted in the literature. Thus, Jones,[2] after analyzing such a series, concluded "that we stand in great need of a large series of cases of (cerebral) vascular lesions, the history of which has been

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1. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133 (May) 1932. Penfield, W.: Surgical Treatment of Spontaneous Cerebral Hemorrhage, Canad. M. A. J. **28**:369, 1933.

2. Jones, A. E.: The Onset of Hemiplegia in Vascular Lesions, Brain **28**:527, 1905.

critically studied, and the evidences of the lesion before and after death carefully recorded." We have attempted to follow this method in the present study and have selected 245 cases from the records of the Boston City Hospital for the last ten years. Many of the patients admitted to the hospital in the past six years were examined by one or both of us. We found acceptable for this analysis 116 cases of cerebral hemorrhage, 106 cases of cerebral thrombosis and 23 cases of cerebral embolism. The smallness of this series is due to the fact that a number of cases had to be excluded for various reasons, the most important being the lack of an adequate history (despite the fact that a signed necropsy permit was always obtained from the nearest relative) and an incomplete clinical record in which findings probably evident on examination of the patient were not included. These are always the difficulties met with in the use of hospital records for research. Records of many of the cases are not as complete as could be desired, but they suffice for the topic at hand.

The clinical differentiation of cerebral hemorrhage from cerebral thrombosis is not always simple, notwithstanding the present widespread use of the lumbar puncture. The examination of the cerebrospinal fluid is an important factor, but only as an adjunct to a careful evaluation of the history and a thorough physical and neurologic examination. We wish to stress that a carefully taken history and its skilful interpretation are the most important factors not only in the differentiation between cerebral hemorrhage and cerebral thrombosis but also in their differentiation from other cerebral lesions. At times this is a vital matter and may be the only factor at one's disposal for the differentiation of these lesions from (traumatic) subdural hemorrhage. As the latter is relievable in practically 100 per cent of cases in which the diagnosis is made within a reasonable time,[3] it is imperative that a thorough history of the patient's illness be obtained as early as possible. In a large general hospital the uniformly poor history of patients presenting evidences of cerebral vascular lesion, especially of those in coma on admission is to be deplored.

ANALYSIS OF THE CLINICAL DATA

We present an analysis of the data obtained from the records of 245 cases of cerebral vascular lesion. We have included 23 cases of cerebral embolism because embolism must be considered in any differential diagnosis of cerebral hemorrhage and cerebral thrombosis, and although the number of cases is not large, they have provided some interesting points.

3. Munro, D.: The Diagnosis and Treatment of Subdural Hematomata, New England J. Med. **22**:1145 (May 3) 1934.

Sex Incidence.—Our series indicates that men are more subject to cerebral vascular accidents than women. The preponderance of men was greatest in the group with cerebral thrombosis. The sex distribution in the 116 cases of cerebral hemorrhage was 53 per cent men and 47 per cent women. In the 106 cases of cerebral thrombosis 64 per cent of the patients were men and 36 per cent women, and in the 23 cases of cerebral embolus, 61 per cent of the patients were men and 39 per cent women.

Age Incidence.—As shown in table 1, the majority of the cases of cerebral hemorrhage and cerebral thrombosis occurred in the age group from 50 to 80 years. The average age of the patients with cerebral hemorrhage, 59 years, was somewhat lower than that of the patients with cerebral thrombosis, 64 years. This was due to the fact that a fairly large number of cases of hemorrhage (27) occurred in persons in the years from 30 to 50 years, as compared with 8 cases of cerebral

TABLE 1.—*Age Incidence of Cerebral Vascular Lesions in 245 Cases*

Age, Years	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total
10 to 19	1	..	2	3
20 to 29	..	..	2	2
30 to 39	3	1	3	7
40 to 49	24	7	3	34
50 to 59	31	25	6	62
60 to 69	29	37	5	71
70 to 79	22	26	..	48
80 to 89	2	8	1	11
Not recorded	4	2	1	7
	116	106	23	245

thrombosis which occurred in patients in these decades. Also, only 2 of the 11 patients over 80 years of age were in the group with hemorrhage.

The age grouping in the cases of cerebral embolism was not significant. This is explained by the fact that in many cases the embolus arose from the vegetation of the heart valves. The majority of the cases, however, occurred in the age group from 50 to 70 years owing to the frequency of embolism associated with auricular fibrillation in these age groups.

Seasonal Incidence.—The seasonal incidence of onset in our series tends to support Gintrac's [4] and Gowers' [5] statement that the onset of cerebral vascular injury occurs more frequently in the winter than in the summer. Our cases were distributed as shown in table 2. Approx-

4. Gintrac, E.: Traité theorique et pratique de l'appareil nerveux, Paris, Germer-Baillière, 1869, vol. 2, p. 467.

5. Gowers, W. R.: Diseases of the Nervous System, ed. 2, London, J. & A. Churchill, 1893, vol. 2, p. 388.

imately 53 per cent of the cases occurred in the five month period from November to March.

Time of Day and Activity.—The time of day of the onset of the cerebral vascular lesion was not significant. In the cases in which this fact was mentioned the onset was found to be fairly evenly distributed among the twenty-four hours. The activity at the time of onset was noted in 53 cases of hemorrhage, 46 cases of thrombosis and 13 cases of embolism. We considered the activity irrelevant (at church, at the theater, bathing, sitting, reading, talking, doing light housework, walking on the street) in 35 cases of hemorrhage, 28 cases of thrombosis and 5 cases of embolism. In 5 cases of cerebral hemorrhage, 9 of cerebral thrombosis and 5 of cerebral embolism the onset occurred while the patient was in the hospital in bed. In 1 case of embolism

TABLE 2.—*Seasonal Incidence of Cerebral Vascular Lesions in 245 Cases*

	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total	Percentage*
January	12	14	2	28	12.0
February	12	9	3	24	10.3
March	13	13	2	28	12.0
April	12	6	..	18	7.7
May	9	7	1	17	7.3
June	12	9	..	21	9.0
July	4	5	2	11	4.7
August	2	5	2	9	3.8
September	7	7	2	16	6.7
October	7	11	..	18	7.7
November	13	3	6	22	9.4
December	13	7	1	21	9.0
Not recorded	..	10	2	12	...
	116	106	23	245	

* Percentage of the 221 cases in which the date of onset was noted.

the onset occurred postoperatively, and in another embolism occurred seven days after the administration of digitalis was begun in a patient with auricular fibrillation and congestive heart failure, the pulse falling from 130 to 60 within that period. In 7 cases of hemorrhage, 4 cases of thrombosis and 2 cases of embolism the onset occurred during sleep. In 3 cases of hemorrhage, 1 of thrombosis and 1 of embolism the onset occurred while the patient was eating. We carefully searched for mention of physical or emotional stress as a factor in the onset of cerebral vascular lesion. This was noted in 4 cases of hemorrhage. In 2 the onset occurred while the patient was at work; in the third, during the excitement of watching a wrestling match, and in the fourth, a few minutes after the patient was arrested for peddling merchandise on Sunday. In one case of cerebral thrombosis the condition began while the patient was "straining at stool."

Previous Cerebral Vascular Lesions.—A history of previous cerebral vascular injury was obtained in 14 cases of cerebral hemorrhage; in 58 cases there had been no previous cerebral vascular lesion, and

this point was not recorded in 44 cases. In the cases of cerebral thrombosis, 19 patients had a history of previous cerebral vascular lesion, 47 had none, and in 40 cases this point was not recorded. In the cases of cerebral embolism 6 patients had a history of a previous cerebral vascular lesion; in 13 cases there was no history of such a lesion, and in 4 cases this point was not recorded.

Premonitory Symptoms.—Premonitory symptoms were recorded in 22 cases of cerebral hemorrhage. Sixteen of the patients had headache for periods ranging from two days to (with the severe intermittent type) three years. One of these, who had had a headache of two weeks' duration, complained of localized numbness and slight weakness of the left extremities for one week. In 3 cases there had been mental disturbances for months. In 2 cases there had been attacks of dizziness, in 1 for two and in the other for one year. Drowsiness was recorded in 2 cases, in 1 for a period of one year and in another, in which there was also complaint of headache, for two days. In the cases of cerebral thrombosis, in which the premonitory symptoms are supposed to be fairly common, they were recorded in only 8 instances. This may be due in part to the fact that the records of the cases of cerebral thrombosis were generally poorer than those of the cases of cerebral hemorrhage. Neurologic prodromes were noted in 3 cases. In 1 there had been repeated and numerous attacks of tingling and numbness in the right and the left side of the face and the left extremities for five days before the onset of left hemiplegia. During these attacks the patient's speech was incomprehensible, and the left arm and leg would become rigid and then flaccid, with increased tendon reflexes and an extensor plantar response. Between attacks the patient could use the left arm and leg, and the plantar response was normal. A softening of the right half of the pons was observed at autopsy. Similarly, a second patient noted numbness and tingling of his left upper extremity twelve days before the onset of left hemiplegia, and softening was found in the right temporal lobe at autopsy. Dizziness was observed by both of these patients simultaneously with the onset of the sensory disturbance. In a third case generalized weakness was present for five days. In 2 other cases dizziness alone was the prodrome. In 1 case the patient noted drowsiness for five days, and in 2 cases mental signs were observed; mental confusion was noted for one day in the first case and mental confusion with hallucinations for three weeks in the second case. In the cases of cerebral embolism the symptoms of endocarditis were usually present for varying periods before the onset of signs of cerebral involvement. Five patients complained of headache for from one day to (the intermittent severe type) three years. The patient with severe headache for three years also had dizziness for the same period. Another

patient had dizziness for one day. One patient had a chill ten days post partum, one day before the onset of the signs of cerebral embolism.

Type of Onset.—In the differentiation of cerebral hemorrhage and cerebral thrombosis the type of onset (table 3) is important. In our series the onset with immediate unconsciousness was nearly twice as frequent in cases of hemorrhage as in cases of thrombosis. In the 79 cases in which this point was mentioned the patient was in coma in 50.7 per cent of the cases of cerebral hemorrhage at the onset and in 68.1 per cent of the 116 cases at the time of admission to the hospital. In the cases of cerebral thrombosis, the patient was in coma at the onset in 32.6 per cent of the 49 cases in which this point was recorded and on admission to the hospital in 38.6 per cent of the 101 cases in which this fact was recorded. The onset with convulsions was also more frequent with hemorrhage. In 8 cases of hemorrhage (14.8 per cent of the 54 cases in which this point was noted) a convulsion occurred (jacksonian type in 1) at the onset. In 11 cases (9.5 per cent)

TABLE 3.—*Incidence of Headache, Vomiting, Convulsion and Coma at the Onset of Cerebral Vascular Lesions*

	Headache		Vomiting		Convulsion		Coma	
	At Onset	In Hospital	At Onset	In Hospital	At Onset	In Hospital	At Onset	On Admission
Cerebral hemorrhage..	26	13	19	14	8	11	35	79
Cerebral thrombosis...	3	2	3	2	2	6	16	39
Cerebral embolism.....	6	4	4	2	2	1	5	9

convulsions occurred (jacksonian type in 1) after the patient's admission to the hospital. Of these 11 cases convulsions occurred also at the onset in 3. Therefore, in 16 cases (13.8 per cent) of cerebral hemorrhage convulsions were known to have occurred at the onset of the hemorrhage or after the patient's admission to the hospital. In 8 of these blood was noted in the ventricles, in 2 there was subarachnoid bleeding and in 2 no subarachnoid or ventricular bleeding was seen. This point was not recorded in the 4 remaining cases. The relationship of convulsive seizures to the site of the lesion and to the presence of syphilis is of considerable significance. In 11 of the cases of cerebral hemorrhage with convulsions bleeding occurred in or near the cortex, frontal, parietal or both. In 4 cases the hemorrhage was in the basal ganglions. The remaining case was one of hemorrhage into the left lateral ventricle diffusing into the midbrain. In only 1 of the 16 cases was the presence of syphilis proved; this was in a patient with a hemorrhage into the basal ganglions. The total number of cases of cerebral thrombosis in which convulsions were present at some time during the course of illness was 7, or 6.6 per cent (in 1 case convulsions occurred

with the onset and after the patient's admission to the hospital). Two patients with embolism had convulsions at the onset, and 1 had convulsions at the onset and after being admitted to the hospital. In 4 cases of cerebral thrombosis with convulsions the lesion was in the motor cortex, in 2 in the basal ganglions and in 1, in the pons. Four of the 7 patients had syphilis, 2 with lesions in the motor cortex and 2 with lesions in the basal ganglions. The site of the lesion in the 2 cases of embolism were the cortex of the occipital lobe and the cortex of the parieto-occipital lobes. Neither patient had syphilis.

Broadbent [6] in 1887 noted that vomiting occurred more frequently with cerebral hemorrhage than with other types of vascular lesion in the brain. Vomiting, if present at the onset and if embolism is excluded, is usually indicative of cerebral hemorrhage. Nineteen patients with cerebral hemorrhage (51.3 per cent of the 37 for whom this point was noted) vomited at the onset. In addition, 6 patients whose history at the onset was unknown vomited during their stay in the hospital. In the group with cerebral thrombosis only 3 patients (6.4 per cent of the 47 for whom this point was noted) vomited at the onset. Another patient in whose case the history of the onset was unknown vomited on admission to the hospital. In these 4 patients the following lesions were observed at autopsy: (1) thrombosis of the basilar artery; (2) softening in the temporal lobe, cerebral edema and nephrosis; (3) thrombosis of the internal carotid artery and peptic ulcer, and (4) thrombosis of the posterior branch of the middle cerebral artery. The lesions in the cases of cerebral embolism with vomiting were multiple emboli of the brain and other organs.

The occurrence of severe headache with the onset of a cerebral vascular lesion is strongly in favor of a diagnosis of cerebral hemorrhage. In 26 cases of cerebral hemorrhage (63.4 per cent of the 41 cases in which this fact was mentioned) there was a complaint of headache at the onset. In addition, 1 patient whose history at the onset is unknown had a headache on admission to the hospital. In the group with cerebral thrombosis (6.1 per cent of the 49 cases in which this symptom was recorded) headache was present in only 3 cases at the onset. One patient whose history at the onset is unknown had a headache on admission to the hospital.

Vital Signs.—The initial temperature, pulse rate and respiratory rate are not of much value in the differentiation of cerebral hemorrhage and cerebral thrombosis. Initial readings of the temperature and pulse rate varied in a rather wide range but were practically the same in both groups. Initial respiratory readings were significant, however, in that the Cheyne-Stokes type of respiration and abnormalities in the depth,

6. Broadbent, W.: Med.-Chir. Rev., 1887, p. 335.

rate and sound of respiration were much more frequent in the patients with cerebral hemorrhage than in the patients with cerebral thrombosis. Thus, 11 cases in which the Cheyne-Stokes type of respiration and 27 cases in which other abnormalities of respiration (stertorous, labored, rapid, dyspneic) were noted (38 cases in all, or 32.7 per cent) were found in the group with cerebral hemorrhage. Among the cases of cerebral thrombosis there were 4 (7 per cent) in which the Cheyne-Stokes type of respiration was noted. In the group with cerebral embolus respiratory abnormalities were noted in 6 cases (Cheyne-Stokes type in 3; rapid in 3, or 26 per cent). A practically constant finding in cases of any type of cerebral vascular lesion was the uniform rise of temperature, pulse rate and respiratory rate several hours or days before death occurred, indicating a collapse of the vasomotor and heat-regulating centers.

Heart.—Clinical abnormalities of the heart were found slightly more frequently in the cases of cerebral thrombosis than in those of cerebral hemorrhage. The heart was rarely normal in cases of cerebral embolism. The heart was clinically enlarged in 84 cases and was fibrillating in 4 other cases of cerebral thrombosis. It was recorded as normal in 18 cases. Cardiac abnormalities occurred in 83 per cent of this group. The heart was clinically enlarged in 66 cases of cerebral hemorrhage and was fibrillating in 2 others and irregular in rhythm in 3. It was recorded as normal in 21 cases. Cardiac abnormalities were noted in 77.1 per cent of this group. In the cases of cerebral embolism the heart was recorded as normal in only 1 instance. Enlargement was recorded in 18 cases and fibrillation in 5 of these 18 (abnormalities in 94.7 per cent).

Arteriosclerosis.—Clinical evidence of arteriosclerosis of the peripheral vessels was noted more frequently in the cases of cerebral thrombosis than in those of cerebral hemorrhage. The incidence of arteriosclerosis in the 69 cases of cerebral hemorrhage in which this point was recorded was as follows: none in 10.1 per cent, moderate in 37.7 per cent, and advanced in 52.2 per cent. In the cases of cerebral thrombosis the peripheral vessels were normal in 1 per cent, moderately sclerotic in 22.3 per cent and markedly sclerotic in 76.7 per cent of the 95 cases in which the point was noted. In the 13 cases of embolism in which the degree of arteriosclerosis was recorded none was noted in 30.7 per cent and it was moderate in 30.7 per cent and advanced in 38.6 per cent.

Blood Pressure.—The comparison of systolic and diastolic blood pressure in our series of cases of cerebral hemorrhage and cerebral thrombosis is given in tables 4 and 5. A glance at the figures in tables 4 and 5 shows that the average systolic and diastolic blood pressure is somewhat higher in persons with cerebral hemorrhage than in those

with cerebral thrombosis. The figures are in number of cases, but they can be used as percentage figures, so closely do the numbers of cases in which the blood pressure was recorded approach 100 (cerebral hemorrhage, 107; cerebral thrombosis, 96).

Eyes.—The type and frequency of pupillary findings in cases of cerebral vascular lesion are moot points, probably because of the changes which occur at various stages of the clinical picture. The findings recorded in table 6 were noted on the first examination at the time of the patient's admission to the hospital. In nearly all the cases this was the only examination of the pupils recorded. In the patients with proved syphilis (of whom there were 15 in the group with hemorrhage, 18

TABLE 4.—*Comparison of the Systolic Blood Pressure in 222 Cases of Cerebral Vascular Lesion*

Systolic Blood Pressure	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
80 to 99	1	0	3
100 to 139	10	11	6
140 to 159	11	17	6
160 to 199	42	43	3
200 to 279	43	25	1
Total	107	96	19

TABLE 5.—*Comparison of the Diastolic Blood Pressure in 222 Cases of Cerebral Vascular Lesion*

Diastolic Blood Pressure	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
40 to 79	12	15	8
80 to 99	25	31	6
100 to 139	58	41	5
140 to 179	12	9	..
Total	107	96	19

in the group with thrombosis and 1 in the group with embolism) the pupils were of normal size in 16 and small in 3, and controlateral dilatation, homolateral dilatation, inequality, irregularity and large and pinpoint sizes were noted in 1 case each. In 9 cases the size was not recorded. The reaction of the pupils to light in 15 patients with syphilis was normal; in 7 the pupils were fixed to light; in 3 they reacted sluggishly, in 1 they reacted slightly, and in 8 the reaction was not noted.

It is known that advanced age alone affects the size and reaction of the pupils, so we attach no great significance to minor changes in the size and reaction of the pupils of the patients in our series. It is of interest, however, to observe the number of cases in which there was dilatation of the pupil on the side opposite that of the cerebral lesion. It was present in 25.5 per cent of the cases of cerebral hemor-

rhage and in 7.4 per cent of the cases of cerebral thrombosis in which the condition was recorded, exclusive of the cases of proved syphilis (table 6). It is also evident that the total loss of pupillary reaction to light is significant. This occurred in 32.1 per cent of the cases of cerebral hemorrhage and in 9.3 per cent of the cases of cerebral thrombosis (exclusive of the cases of proved syphilis) in which the reaction of the pupils was noted.

Conjugate deviation of the eyes alone or of the head and eyes together occurred in 18 cases of cerebral hemorrhage; in 15 of these the deviation was toward the side of the cerebral lesion and in 3 cases away from it. Conjugate deviation was recorded in 7 cases of cerebral thrombosis; in 6 of these the deviation was toward the side of the cerebral lesion and in 1 case away from it. In 1 case of cerebral embolism deviation was noted toward the side of the cerebral lesion.

TABLE 6.—*Pupillary Size and Reactions in Cases of Cerebral Vascular Lesion**

	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Size			
Normal	23	36	16
Dilated (homolateral)	2	2	..
Dilated (controlateral)	22	5	1
Dilated (bilateral)	4	..	..
Small	16	8	1
Pinpoint	5	3	..
Reaction to Light			
Normal	41	45	14
Sluggish	12	12	2
Fixed	26	6	2
One fixed, one normal	2	1	..

* The cases in which syphilis was presented were not included.

Stiffness of the Neck.—Stiffness of the neck is an important differential sign between cerebral hemorrhage and cerebral thrombosis. It was present in 55.1 per cent of the cases of cerebral hemorrhage in which this point was recorded and in only 7 per cent of the cases of cerebral thrombosis. This 7 per cent represents 4 cases, in 1 of which there was evidence of meningeal and vascular syphilis and xanthochromic cerebrospinal fluid. Thrombosis of the internal carotid and middle cerebral arteries on one side was noted at autopsy. In the remaining 3 cases there was high normal or increased pressure in the spinal fluid (from 190 to 240 mm. of water). At autopsy thrombosis of the internal carotid artery was noted in 1 case and in the remaining 2 softenings in the basal ganglions were seen. It is evident that bleeding into the spinal fluid produces meningeal irritation which manifests itself by the usual sign of stiffness of the neck. This is a valuable sign in the differentiation of cerebral hemorrhage and cerebral thrombosis.

Hemiplegia.—In our series left hemiplegia (107 cases) occurred more frequently than right hemiplegia (78 cases). The occurrence of quadriplegia is presumptive evidence of cerebral hemorrhage. Four of the 6 patients with quadriplegia had cerebral hemorrhage, 1 had cerebral thrombosis and 1 cerebral embolism.

Aphasia.—Aphasia was noted in 50 of the 105 patients who were conscious enough for its presence to be determined. Six of these 50 patients had left hemiplegia.

Mental Signs.—Mental signs were slightly more common in the group with cerebral thrombosis than in the group with cerebral hemorrhage (60.3 per cent of 73 cases as compared to 53.6 per cent of 41 cases in which this point was recorded). We did not believe it worth while to correlate the mental signs with the site of the lesion because of complicating factors, for example, cerebral arteriosclerosis. Coma interfered with this determination in 59 cases of cerebral hemorrhage and in 27 cases of cerebral thrombosis.

Plantar Signs.—In the group of cases of cerebral hemorrhage the bilateral occurrence of Babinski's sign was found twice as frequently as in those of cerebral thrombosis. In the cases of cerebral hemorrhage Babinski's sign was noted unilaterally in 40.2 per cent and bilaterally in 27.8 per cent of the 97 cases in which this test was recorded. In the group of cases of cerebral thrombosis the sign was noted unilaterally in 58 per cent and bilaterally in 14.7 per cent of the 88 cases in which the test was recorded.

Progression.—An increase in signs, or signs of progression of the cerebral vascular lesion after the onset, is an important differential point. What is meant by signs of progression can best be illustrated by typical cases.

In case 40 of the cerebral hemorrhage group the patient noted a sudden onset (during excitement) of a "hot feeling" passing over the forehead and behind the eyeballs followed by numbness of the left side of the face and the left upper extremity. The patient felt ill, went outside for air, felt faint and took a taxicab to go home. In the taxicab the patient became nauseated and vomited, and shortly thereafter the left extremities felt stiff. She was carried into her room semiconscious. The entire episode occupied about one hour.

Case 99 of the cerebral hemorrhage group noted a progression of somewhat longer duration. He experienced a sudden onset of lethargy, loss of energy and frontal headache on the left side, which was continuous. One week later he was seen to carry the left upper extremity in a flexed position, supported by his right hand. It was not known when this weakness occurred. He complained of attacks of numbness in the left extremities. Eight or nine days after the onset his speech became somewhat dysarthric. One day later the left upper extremity became numb, tingled somewhat and twitched occasionally. Immediately thereafter the entire left side became numb. One hour later he was taken to a physician's office.

After leaving the office he became disoriented and lapsed into a semicomatose state. Complete paralysis of the left arm and leg followed shortly thereafter. In this case the period of progression of signs was ten days.

This type of progression of signs is much more often seen in cases of cerebral hemorrhage; progression occurred in 18.7 per cent of the 112 cases in which this point was recorded, as compared with 2 per cent of the cases of cerebral thrombosis. In only 1 case was progression (of one day's duration) noted in the cases of cerebral embolism. The duration of these signs of progression in the cases of hemorrhage was from one-half hour to ten days. In the 2 cases of thrombosis signs of progression lasted for seven hours and two days, respectively. It is not uncommon in cases of lesions of the medulla and pons to note paresthesia ushering in the attack (Merritt and Finland[7]). In only 3 of these 24 cases in which there was progression was the midbrain or pons involved. These signs of progression which develop after the

TABLE 7.—*Length of Survival in 245 Cases of Cerebral Vascular Lesion*

Length of Life After Onset	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Less than 12 hr.	5	0	0
12 to 24 hr.	4	1	0
1 to 4 days	48	26	8
5 to 14 days	44	35	8
2 wk. to 2 mo.	13	21	4
2 mo. to 6 mo.	1	6	1
6 mo. to 7 yr.	0	7	1
Unknown	1	10	1
	116	106	23

onset of the cerebral vascular lesion are not to be confused with premonitory symptoms. The former are severe and are usually localizable to some area in the brain.

Period of Survival.—The length of survival is of importance in the differentiation of cerebral hemorrhage and cerebral thrombosis. In table 7 the length of survival of the patients in our series is indicated.

The shortest periods of survival occurred in the cases of cerebral hemorrhage: One patient lived only three hours after the onset, 2, eight hours, and 2, twelve hours. The longest period of survival in a case of cerebral hemorrhage was eighty-one days. Eighty-seven and eight-tenths per cent of the patients with cerebral hemorrhage died within two weeks. The shortest period of survival in our cases of cerebral thrombosis was twelve hours, the longest, seven years. Sixty-four and five-tenths per cent of the patients with cerebral thrombosis for whom the length of survival was known died within two weeks.

7. Merritt, H. H., and Finland, M.: Vascular Lesions of the Hind-Brain, Brain **53**:290, 1930.

From observations on this series and from our experience we agree with the numerous authors [8] who have expressed the belief that death does not occur suddenly (within minutes) after the onset of a cerebral vascular lesion. We also support the statement of Cadwalader [8b] and of Robinson [8d] that a cerebral hemorrhage of an appreciable size is probably always fatal.

Urine.—The presence of albumin or casts in the urine was noted in 67.9 per cent of the 78 cases of cerebral hemorrhage in which an examination of the urine was made. This is slightly greater than the 52.7 per cent of the 74 cases of cerebral thrombosis. Sugar was observed in the urine in 10.2 per cent of the 78 cases of cerebral hemorrhage and in 8 per cent of the 94 cases of cerebral thrombosis.

Blood.—A white blood count was made on the patient's admission to the hospital in 165 of the cases of cerebral hemorrhage and cerebral thrombosis. The results varied between 40,000 and 5,000 per cubic millimeter. In 54.6 per cent of the uncomplicated cases of cerebral hemorrhage the count was over 12,000 per cubic millimeter as compared with 10.1 per cent of the cases of cerebral thrombosis with no complications. The highest count in the cases of cerebral thrombosis with no complication was 18,800.

Nonprotein Nitrogen.—The nonprotein nitrogen content of the blood was determined in 107 cases. It was normal in 68 cases, moderately elevated (from 46 to 75 mg.) in 24 cases and markedly elevated (from 76 to 200 mg.) in 9 cases. There was no difference in the incidence of elevation of the nonprotein nitrogen content in the cases of cerebral hemorrhage and that in the cases of cerebral thrombosis.

Glycosuria and Hyperglycemia.—The occurrence of sugar in the urine in patients with a cerebral vascular lesion has been frequently commented on. Sixteen of our patients had glycosuria on admission to the hospital. Only 3 of these patients had a history of diabetes mellitus, and in the majority of the cases subsequent examinations of the urine gave negative results for sugar. Determinations of the sugar content of the blood were made in 40 cases. In 15 cases the sugar

8. (*a*) Cadwalader, W. B.: A Comparison of the Onset and the Character of the Apoplexy Caused by Cerebral Hemorrhage and by Vascular Occlusion, J. A. M. A. **62**:1385 (May 2) 1914. (*b*) Moloney, M. F.: Sixty Cases of Sudden or Violent Death, Dublin J. M. Sc., Feb. 1921, p. 68. (*c*) Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 1238. (*d*) Robinson, G. W.: Encapsulated Brain Hemorrhages, Arch. Neurol. & Psychiat. **27**:1441 (June) 1932. (*e*) Spiller, W. G.: The Duration of Life After Extensive Hemorrhage of the Brain, J. A. M. A. **51**:2101 (Dec. 19) 1908. (*f*) Spilsbury, B. H.: Sudden Death, Practitioner **98**:132, 1917. (*g*) Thomas, H. M., in Osler, William, and McCrae, Thomas: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 5 p. 452. (*h*) Winkelman, N. W., and Eckel, J. L.: Extensive Brain Hemorrhage, J. Nerv. & Ment. Dis. **61**:592, 1925.

content of the blood was normal (from 51 to 120 mg. per hundred cubic centimeters). In 9 there was slight hyperglycemia (from 120 to 160 mg.) and in 15 there was moderate or marked hyperglycemia (from 160 to 350 mg.). Two of the patients of this group are known to have diabetes. It is obvious that transient hyperglycemia and glycosuria are not infrequent in patients with a cerebral vascular lesion. It is probably due to a temporary disturbance in the sugar metabolism as a result of the cerebral injury. It is apparently not related to the site of the lesion, but it is noted more frequently in patients with hemorrhage than in those with thrombosis or embolism.

Syphilis in Patients with a Cerebral Vascular Lesion.—Thirty-four of our patients had serologic evidence of a syphilitic infection. The cases were divided as follows: cerebral hemorrhage, 15 cases (positive Wassermann reaction of the blood in 8 cases, of the cerebrospinal fluid in 3 and of both the blood and the cerebrospinal fluid in 4); cerebral thrombosis, 18 cases (positive Wassermann reaction of the blood in

TABLE 8.—*Cerebrospinal Fluid Pressure in 120 Cases of Cerebral Vascular Lesion*

Pressure, Mm. of Fluid	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Below 200	26	38	9
200 to 300	12	9	0
301 to 400	12	2	1
401 to 1,100	11	0	0
Total	61	49	10

12 cases, of the cerebrospinal fluid in 2 and of the blood and the cerebrospinal fluid in 4), and cerebral embolus, 1 case (positive reaction of the blood). All the patients with cerebral hemorrhage who gave a positive reaction of the blood had a moderate or marked degree of hypertension. This was not true of the patients with cerebral thrombosis or of the patient with cerebral embolism.

Cerebrospinal Fluid.—A lumbar puncture was performed in 145 of our cases. The observations on the cerebrospinal fluid are important in the differential diagnosis of cerebral hemorrhage and cerebral thrombosis. The pressure and the appearance of the fluid are the two most significant findings. Pressure greater than 400 mm. of cerebrospinal fluid was found only in patients with cerebral hemorrhage, and a frankly bloody fluid is indicative of cerebral hemorrhage. The pressure readings in the 120 cases in which it was recorded are given in table 8.

In 37.7 per cent of our cases of cerebral hemorrhage the pressure was greater than 300 mm. of cerebrospinal fluid, whereas in only 4 per cent of the cases of cerebral thrombosis was such a pressure recorded. In 18 per cent of the cases of cerebral hemorrhage the pressure was greater than 400 mm. Pressure greater than 400 mm. was not recorded

in any case of cerebral thrombosis. This is in agreement with the findings of Krabbe and Geert-Jörgenson.[9]

The appearance of the fluid is very important. A frankly bloody fluid is indicative of cerebral hemorrhage. As shown in table 9, in 74 per cent of the 68 cases of cerebral hemorrhage frankly bloody cerebrospinal fluid was noted. In only 1 of the 64 cases of cerebral thrombosis was bloody fluid noted. There were 7,000 red blood cells per cubic millimeter in this specimen. It was impossible to determine from the records whether the blood in this specimen was due to faulty technic in the performance of the puncture. Examination of the brain at necropsy did not reveal any evidence of blood in the cerebral ventricles or the subarachnoid space. The presence microscopically of a few red blood cells was not uncommon in the cerebrospinal fluid of the patients with cerebral thrombosis, and slight xanthochromia without the presence of blood was noted just as frequently in this group as in the patients with cerebral hemorrhage.

TABLE 9.—*Appearance of the Cerebrospinal Fluid in 145 Cases of Cerebral Vascular Lesion*

Appearance	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Bloody	49	1	2
Xanthochromic	5	6	2
Cloudy	1	0	1
Clear	13	57	8
Total	68	64	13

Two of the patients with cerebral embolism had frankly bloody fluid. This was probably due to the rupture of small mycotic aneurysms.

An analysis of the white cells in the cerebrospinal fluid was of interest in that it revealed that a moderate or marked degree of aseptic meningeal reaction was much more common in the cases of cerebral hemorrhage than in those of cerebral thrombosis. As had been previously pointed out by one of us (H. H. M.[10]), this cellular response in the cerebrospinal fluid in patients with cerebral hemorrhage is due to an aseptic meningeal reaction to an area of necrosis near the ventricles. The white cell count in the cerebrospinal fluid in 70 cases of cerebral vascular lesion is given in table 10. Cases in which the cerebrospinal fluid was bloody as well as cases in which the Wassermann reac-

9. Krabbe, K. H., and Geert-Jörgenson, E.: Recherches sur la pression rachidienne et sur le liquide céphalo-rachidien dans les hémorrhagies et les thromboses du cerveau, Acta psychiat. et neurol. **6**:529, 1931.

10. Merritt, H. H., and Moore, M.: Tumours of the Brain Associated with Marked Pleocytosis in the Cerebrospinal Fluid, J. Neurol. & Psychopath. **13**:118, 1932.

tion was positive in the blood or cerebrospinal fluid are not included in this table.

In 2 cases of cerebral hemorrhage between 100 and 1,000 white cells per cubic millimeter were present in the cerebrospinal fluid at the first puncture. In 2 other cases subsequent punctures disclosed 1,900 and 3,600 white cells, respectively. In the specimens of fluid with a high white cell count polymorphonuclear leukocytes were the predominating cell type. The occurrence of a large number of white cells is often noted in the cerebrospinal fluid of patients with septic cerebral emboli. This is due to an aseptic meningeal reaction to the septic focus in the brain.

The protein content of the cerebrospinal fluid was usually normal or only moderately elevated in the clear or xanthochromic fluids. A protein content greater than 100 mg. per hundred cubic centimeters occurred in only one specimen of nonbloody fluid (in a case of cerebral

TABLE 10.—*White Blood Cell Count of the Cerebrospinal Fluid in 70 Cases of Cerebral Vascular Lesion* *

Cells, per Cu.Mm.	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total
0 to 5	9	36	4	49
6 to 10	1	2	2	5
11 to 50	2	4	2	8
51 to 100	0	1	1	2
101 to 1,000	2	0	2	4
1,000 to 4,000	0	0	2	2
	14	43	13	70

* All cases are excluded in which bloody fluid or positive Wassermann reaction of the blood or cerebrospinal fluid were noted.

thrombosis). The specimens of bloody fluid from patients with cerebral hemorrhage usually had from 200 to 3,000 mg. of protein per hundred cubic centimeters, depending largely on the amount of blood serum present in the cerebrospinal fluid.

The sugar content of the cerebrospinal fluid was determined in 25 cases and was found to be normal or slightly increased. The chloride content was determined in 19 cases and was normal or only slightly decreased in all.

The colloidal gold curve of the cerebrospinal fluid has no differential value in the diagnosis of cerebral vascular lesions. The colloidal gold reaction was tested in 35 of the specimens of fluid from patients with a cerebral hemorrhage. Abnormal curves (first zone, midzone and end-zone curves) were found in the specimens from 21 patients (60 per cent). Three of the 21 patients had a proved syphilis, and a majority of the remainder had bloody cerebrospinal fluid, which would account for the changes in the colloidal gold reaction. Abnormal colloidal gold curves were found in the cerebrospinal fluid of 18 of 45 patients with

cerebral thrombosis. Five of the patients whose colloidal gold curve was abnormal had proved syphilis. There were three normal and three abnormal reactions to the colloidal gold test in specimens of fluid from patients with cerebral embolism.

NECROPSY OBSERVATIONS

Cause of Death.—The cause of death (as determined at autopsy) was as follows: In the group of cases of cerebral hemorrhage death was due to hemorrhage alone in 41 instances. Contributory causes were bronchopneumonia in 45 cases, heart failure in 15, uremia in 5, lobar pneumonia in 3, pulmonary infarct in 3, and diabetes mellitus, lymphoblastoma, vegetative endocarditis and pulmonary tuberculosis in 1 case each. In the cases of cerebral thrombosis the thrombosis alone was the cause of death in 30 instances. Contributory causes were: bronchopneumonia in 41 cases, heart failure in 19, lobar pneumonia in 5, uremia in 3, pulmonary tuberculosis in 2, carcinoma in 2 and pulmonary

TABLE 11.—*Protein Content of the Cerebrospinal Fluid in 53 Cases of Cerebral Hemorrhage and Thrombosis* *

Protein Content, Mg. per 100 Cc.	Cerebral Hemorrhage	Cerebral Thrombosis	Total
Under 45	5	22	27
46 to 75	6	14	20
76 to 100	1	4	5
100 to 200	0	1	1
	12	41	53

* All cases are excluded in which bloody fluid or a positive Wassermann reaction of the blood or cerebrospinal fluid was noted.

infarct, alcoholism, necrosis of the pancreas and staphylococcic meningitis in 1 each. Cerebral embolism alone was the cause of death in 7 cases. Contributory causes were: vegetative endocarditis in 10 cases, coronary thrombosis in 2 and bronchopneumonia, heart failure, pulmonary infarct and mesenteric thrombosis in 1 each.

Body Build.—The state of nutrition was noted in 111 cases of cerebral hemorrhage. Twenty-seven per cent of the patients were obese, and 16.2 per cent were poorly nourished or emaciated. The remaining 56.8 per cent were well nourished. In the 104 cases of thrombosis in which this condition was recorded 15.2 per cent of the patients were obese, 28 per cent were poorly nourished or emaciated and the remaining 56.8 per cent were normal.

Heart.—The size of the heart was recorded in 99 of the cases of cerebral hemorrhage; there was moderate or marked hypertrophy in 88 per cent. This is in agreement with Herxheimer and Schulz'[11]

11. Herxheimer, G., and Schulz, K.: Statistisches zum Kapitel Bluthochdruck, Herzhypertrophie, Nierenarteriolosklerose, Gehirnblutung nach anatomischen Befunden, Klin. Wchnschr. **10**:433, 1933.

figure (91 per cent). The size of the heart was recorded in 87 cases of cerebral thrombosis; enlargement was present in 84 per cent.

Arteriosclerosis.—Examination of the aorta was recorded in 98 cases of cerebral hemorrhage. The aorta was normal in only 9 per cent. It showed evidence of moderate arteriosclerosis in 57 per cent and marked arteriosclerosis in 34 per cent. The condition of the aorta was recorded in 91 cases of cerebral thrombosis. It was normal in 8 per cent, moderately sclerotic in 46 per cent and markedly sclerotic in 42 per cent, and in 4 cases there was syphilitic aortitis.

Coronary sclerosis, moderate or advanced, was present in 61 (73 per cent) of the 84 cases of cerebral hemorrhage in which the condition of the coronary vessels was noted. Coronary sclerosis was found in 81 per cent of the 81 cases of cerebral thrombosis in which the condition of the coronary vessels was noted.

Kidneys.—Gross evidence of lesions in the kidneys was recorded in 42 cases of cerebral hemorrhage (infarcts, 2; chronic nephritis, 15; chronic vascular nephritis, 22, and polycystic kidney, 3), in 40 cases of cerebral thrombosis (infarcts, 2; chronic nephritis, 15; chronic vascular nephritis, 19; polycystic kidney, 1; pyelonephritis, 2, and pyelitis, 1) and in 18 cases of cerebral embolism (infarcts, 16; chronic nephritis, 1, and polycystic kidney, 1).

Cerebral Arteriosclerosis.—Arteriosclerosis of the cerebral vessels was practically a constant finding in the cases of cerebral thrombosis, in contrast to the condition of the vessels in the cases of cerebral hemorrhage, in 21 per cent of which the vessels were normal. Sclerosis of the cerebral vessels in the 81 cases of cerebral hemorrhage in which this point was noted was recorded as follows: advanced sclerosis in 45.7 per cent, and moderate sclerosis in 33.3 per cent. In the remaining 21 per cent the cerebral vessels showed little or no sclerosis (normal). Among the 78 cases of cerebral thrombosis in which this point was recorded, advanced arteriosclerosis was noted in 74.3 per cent and moderate arteriosclerosis in 23 per cent. The patients in the two remaining cases (2.4 per cent) had proved syphilis, and the cerebral vessels were grossly normal at autopsy. In 6.2 per cent (1 case) of the 16 cases of cerebral embolism the cerebral vessels showed advanced sclerosis; in 50 per cent they showed moderate sclerosis, and in the remaining 43.8 per cent they were normal.

Blood in the Ventricles and Subarachnoid Space.—In the 98 cases of cerebral hemorrhage in which this point was recorded blood was present in the cerebral ventricles in 66.3 per cent and in the subarachnoid space in 9.1 per cent. In the remaining 24.6 per cent neither ventricular nor subarachnoid bleeding was noted. In none of the 106 cases of cerebral thrombosis was blood noted in the ventricular or in the subarachnoid

spaces. In the 23 cases of cerebral embolism blood was found in the ventricles in 1 (4.3 per cent) and in the subarachnoid space in 1. In the remaining 91.4 per cent there was no evidence of subarachnoid or ventricular blood.

Location of Lesion.—In the cases of cerebral hemorrhage single lesions were localized as follows: basal ganglions, 58; entire hemisphere, 6; frontal lobe, 13; parietal lobe, 3; temporal lobe, 9; occipital lobe, 5; ventricle, 1; brain stem, 1; midbrain, 3, and cerebellum, 2.

In the remaining 12 cases (10.3 per cent) there were multiple discrete lesions. In 4 cases each there were 2 cerebral hemorrhages (right half of the cerebellum and left occipital region; right temporal and left occipital area; left basal ganglions and right frontal region, and basal ganglions on both sides). In 7 cases there were hemorrhage and softening (hemorrhage in the right basal ganglions and softening of the left occipital lobe, 2 cases; hemorrhage in the right basal ganglions and softening of the right insula; hemorrhage in the right occipital region and softening of the right internal capsule; hemorrhage in the right side of the pons and softening of the right parietal lobe; hemorrhage in the left basal ganglions and softening of the left external capsule; hemorrhage in the left basal ganglions and softening of the right basal ganglions). In the remaining case hemorrhage occurred into the right basal ganglions and into the pons, and there was softening of the left basal ganglions. In 3 cases the location of the lesion was not recorded.

Single lesions in the cases of cerebral thrombosis were localized as follows: basal ganglions, 38; frontal lobe, 3; parietal lobe, 4; temporal lobe, 6; occipital lobe, 5; brain stem, 3; cerebellum, 2, and midbrain, 1.

In 24 cases (27 per cent) multiple softenings were present, while in the remaining 18 cases there was thrombosis of one or more of the large cerebral vessels, with extensive areas of softening. In 2 cases the location of the lesion was not recorded.

Multiple lesions were the rule in cases of cerebral embolism. In all but 6 of the 23 cases in our series multiple lesions were present (73.9 per cent). In 3 cases these included occlusion of a large cerebral vessel (the basilar artery in 2 cases and the right anterior cerebral artery in 1). In 21 of the cases of cerebral embolism infarcts were present in other viscera, and in the remaining 2 there were vegetative endocarditis with multiple infarcts in the brain.

FREQUENCY OF CEREBRAL VASCULAR LESIONS

Lest the distribution (116 cases of hemorrhage, 106 of thrombosis and 23 of embolism) in our series of cases of cerebral vascular lesions prove misleading, we wish to note what we believe to be a more accurate incidence. We have critically studied the records of cases of cerebral

vascular lesions observed at the Boston City Hospital within the past five years, in many of which the patients were examined by us. These include only those cases in which the diagnosis was reasonably certain, and among them are some of the cases included in our series. Cases are not included unless a lumbar puncture was performed. The cases which we were able to accept for this group (to give us an index of distribution) total 407. The diagnosis of cerebral thrombosis was made in 81.8 per cent of these cases, of cerebral hemorrhage in 15 per cent and of cerebral embolism in the remaining 3.2 per cent. We feel that this is the more probable ratio of incidence of these three types of cerebral vascular lesion. A series controlled by observations at necropsy gives a false ratio between the incidence of cerebral hemorrhage and cerebral thrombosis because a great majority of patients with the latter condition recover to a degree sufficient for discharge from the hospital.

SUMMARY

The use of hospital records of patients admitted with cerebral vascular lesion which cause a fatal outcome in obtaining conclusions has its limitations, chiefly because of the selective nature of the material. Such a selection of cases proved at necropsy is necessary in any attempt to determine the findings which are of value in a differential diagnosis. We have used the records of 245 cases of cerebral vascular lesion as a basis for this study. All of these cases were studied clinically and at necropsy. We have slighted the analysis of the cases of cerebral embolism chiefly because of the few cases and also because of the relative ease with which this diagnosis is made.

1. The average age of the patients with cerebral hemorrhage is slightly lower than that of patients with cerebral thrombosis. Cerebral vascular accidents are rare below the age of 40, but cerebral hemorrhage occurs more frequently in the decade from 40 to 50 than cerebral thrombosis.

2. The symptoms occurring at the onset of the lesion are of considerable aid in the differential diagnosis.

The occurrence of a sudden severe headache or vomiting at the onset is strongly in favor of a diagnosis of cerebral hemorrhage.

Convulsions are more frequent in the cases of cerebral hemorrhage. In our series they occurred in 13.8 per cent of the cases of cerebral hemorrhage and in 6.6 per cent of the cases of cerebral thrombosis. The convulsions which occurred in cases of cerebral thrombosis were usually associated with syphilis or a lesion in the motor cortex.

The onset with immediate unconsciousness is more frequent in cases of cerebral hemorrhage (51 per cent) than in cases of cerebral thrombosis (32 per cent). The presence of coma on the patient's admission

to the hospital is probably a more reliable index to the relative frequency of this symptom (cerebral hemorrhage, 68 per cent; cerebral thrombosis, 39 per cent).

Signs of progression of the cerebral vascular lesion after the onset are more frequent in the cases of cerebral hemorrhage.

3. Abnormalities in the depth, rate, rhythm and sound of the respirations are more frequent in cases of cerebral hemorrhage.

4. The blood pressure ranged somewhat higher in our cases of cerebral hemorrhage. The systolic blood pressure was greater than 200 mm. in 41 per cent of the cases of cerebral hemorrhage, as compared with 26 per cent of the cases of cerebral thrombosis. Cerebral hemorrhage or cerebral thrombosis is not rare in a patient with normal blood pressure.

5. Arteriosclerosis as evidenced by examination of the peripheral vessels and those of the retina occurs more frequently and is more advanced in cases of cerebral thrombosis. There was no evidence of arteriosclerosis in 10 per cent of our cases of cerebral hemorrhage, as compared with 1 per cent of the cases of cerebral thrombosis.

6. Abnormalities in the eyes are found more frequently in cases of cerebral hemorrhage. Conjugate deviation of the eyes (or head and eyes) was found in 15 per cent of our cases of cerebral hemorrhage and in 7 per cent of the cases of cerebral thrombosis. Unilateral dilatation of the pupils (usually on the side opposite the cerebral lesion) occurred in 25 per cent of the cases of cerebral hemorrhage, as compared with 7.4 per cent of the cases of cerebral thrombosis. Total loss of the pupillary light reflex was noted in 32 per cent of the cases of cerebral hemorrhage and in 9 per cent of the cases of cerebral thrombosis. Cases in which the presence of syphilis was proved were excluded from this calculation.

7. Stiffness of the neck is usually indicative of a cerebral hemorrhage. It was found in 55 per cent of the cases of cerebral hemorrhage and in only 7 per cent of the cases of cerebral thrombosis.

8. The bilateral occurrence of the Babinski sign was noted almost twice as often in the cases of cerebral hemorrhage (28 per cent) as in the cases of cerebral thrombosis (15 per cent).

9. The initial leukocyte count in cases of cerebral hemorrhage with no complications is often very high. The count was markedly increased in 55 per cent of our cases of cerebral hemorrhage, as compared with 10 per cent of our cases of cerebral thrombosis with no complications.

10. The findings at lumbar puncture are of great aid in the differential diagnosis between cerebral hemorrhage and cerebral thrombosis. The cerebrospinal fluid pressure was increased in 57 per cent of our cases of

cerebral hemorrhage and in 22 per cent of the cases of cerebral thrombosis. In 38 per cent of the cases of cerebral hemorrhage the cerebrospinal fluid pressure was greater than 300 mm., and in 18 per cent the pressure was greater than 400 mm. In the cases of cerebral thrombosis a pressure greater than 300 mm. was rare and pressure greater than 400 mm. did not occur.

A grossly bloody fluid was found in 74 per cent of the cases of cerebral hemorrhage, and it was rarely, if ever, found in cases of cerebral thrombosis.

11. The period of survival is usually shorter in cases of cerebral hemorrhage than in those of cerebral thrombosis. In 50 per cent of the cases of cerebral hemorrhage the patient died within four days of onset, and in only 28 per cent of the cases of cerebral thrombosis did the patient die in this period. Cerebral vascular lesions do not cause sudden death.

CONCLUSION

The differential diagnosis between cerebral hemorrhage and cerebral thrombosis can usually be made during life. A carefully taken history of the onset and progress is of paramount importance. A thorough analysis of the history, together with the results of the physical and neurologic examinations and of the examination of the cerebrospinal fluid, should make the differentiation possible in nearly 100 per cent of the cases.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART II

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DISEASES OF THE PULMONARY VESSELS

HISTORY

Excellent historical accounts have been given by Costa,[63] Giroux,[114] Posselt [240] and others, so a brief sketch will suffice here.

Pulmonary arteriosclerosis was recognized early in the last century by Brisson (1803), Andral (1829), Lobstein (1835) and others, but it was thought to be rare. Dietrich (1850) first recognized its frequency in cases of mitral stenosis and emphysema. Posselt [240] collected all the reports of cases (274) published in the nineteenth century and showed that in 40 per cent of the cases mitral stenosis was present and that in the great majority of the rest there were various other types of heart disease. Emphysema, he thought, was not a cause. The chief cause was a high pulmonary arterial pressure, though infections, intoxications and congenital inferiority of the pulmonary arteries also played a part. In 1908 he [239] described, on the basis of 10 of his own cases, the clinical picture that he thought was characteristic of pulmonary arteriosclerosis. Comparatively little has been added to the accepted symptomatology since.

In the present century new forms of disease of the pulmonary arteries have been differentiated. "Primary pulmonary arteriosclerosis," in which no obvious cause for the sclerosis can be found, has been separated from the main group of "secondary pulmonary sclerosis," in which there is some obvious cardiac or vascular cause for the increased pulmonary arterial blood pressure. Interest in primary sclerosis was first aroused by the reports of Romberg (1891) and Aust (1892), though cases possibly of this type had been described by Klob (1865), Crudeli (1868) and Wolfram (1883). Many cases have been reported since, though in most of them the correctness of the diagnosis is doubtful.

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

Since several types of lesions are found in the pulmonary vessels, it is probable that it will be necessary to subdivide the cases of primary sclerosis.

The concept of "Ayerza's disease," elaborated by the Argentinian school, has attracted a great deal of notice. The meaning of the term "Ayerza's disease" varies with each author who uses it. Generally it signifies a condition in which the patient has heart failure with intense cyanosis and at autopsy is found to have syphilis of the pulmonary arteries and possibly also of the lungs and bronchi. Reasons will be given later in the appropriate section for doubting the specificity of this syndrome.

It has long been known that subacute bacterial endarteritis may attack the pulmonary arteries in cases of congenital heart disease, especially when there is a patent ductus arteriosus. In 1917 Lutembacher [183] described acute, subacute or chronic endarteritis of large and medium-sized branches of the pulmonary artery in cases of mitral stenosis and held this responsible for the fever and rapid downhill course in some cases. This process, together with infection of the edematous fluid in the pulmonary alveoli, has been thought [52] to be responsible for the pyrexial attacks in patients with congestive heart failure. Pappenheimer (1924), Kugel (1928), Chiari (1930) and others have shown that rheumatic fever may injure both large and small branches of the pulmonary artery. Laubry and Thomas (1925, 1926, 1927) and many others have insisted on the importance and frequency of syphilis of the pulmonary arteries. The frequency of thrombosis of the pulmonary arteries, often with little apparent embarrassment of the circulation, has been stressed by Billings (1921), Møller (1922), Brenner (1931) and others. Laubry (1922) reported cases which he thought demonstrated the importance of compression of the pulmonary artery, e. g., by enlarged mediastinal glands, in the production of failure of the right heart.

It is thus clear that a great variety of lesions of the pulmonary artery are now recognized and that several different symptom complexes are with more or less justification ascribed to them.

SCHEME OF THE PRESENT INVESTIGATION

Most of the large number of papers on diseases of the pulmonary vessels have consisted of reports of single cases, without controls, from which sweeping conclusions have often unjustifiably been drawn. Steinberg [284] made macroscopic observations on the pulmonary arteries in 500 consecutive autopsies, but a study of this type is inadequate as many lesions even in the larger branches are missed and the small vessels cannot be examined except microscopically. Costa [g] studied the pul-

(*g*) 63, 64.

monary vessels microscopically in 210 unselected autopsies, but he was interested only in arteriosclerosis and his attention was fixed especially on the stem of the pulmonary artery and its larger branches. Ljungdahl [176] considered the question only from the standpoint of the incidence of pulmonary arteriosclerosis in various types of cardiac and pulmonary disease. It was felt that before all this mass of accumulated data could be of use it was necessary to provide a background of carefully controlled observations. The study here reported was undertaken as a contribution toward that end.

In 100 consecutive unselected autopsies a careful macroscopic examination was made of the main extrapulmonary pulmonary arteries and veins and of the pulmonary arterial branches as far as they could be opened up with fine scissors. The circumference of the stem of the pulmonary arteries was measured 2 cm. above the cusps and compared with that of the aorta. The circumference of the right and left arteries at the hilus and of the pulmonary veins at their junction with the left auricle was also measured.

Microscopic sections of all portions of the pulmonary vascular bed were examined, namely, transverse sections of the stem of the pulmonary artery 2 cm. above the cusps; longitudinal sections of the root of the stem, including the pulmonary valve and a portion of the right ventricle; transverse sections of the main extrapulmonary arteries and of the main extrapulmonary veins just proximal to their junction with the left auricle; the large elastic intrapulmonary arteries; and the small muscular arteries, arterioles, venules, capillaries and veins of all sizes. For the examination of the intrapulmonary vessels sections were taken from all the lobes of each lung and usually both from near the hilus and from the periphery so as to insure obtaining both large and small vessels. The sections were stained by each of the following methods: (1) methylene blue and eosin, (2) Mallory's phosphotungstic hematoxylin, (3) Mallory's connective tissue stain and (4) Verhoeff's elastic tissue stain and Van Gieson's stain. The thickness of each of the three coats of the extrapulmonary vessels was measured by means of an ocular micrometer. Many of the intrapulmonary vessels in each of the categories previously mentioned were examined and measured. Records were made of any pathologic changes, together with the external diameter of the vessel, the diameter of its lumen and the thickness of each of its coats. The pathologic changes in the pulmonary vessels were correlated with those in the other organs, particularly the heart and lungs, and with those in the systemic vessels, studied by means of sections of the organs stained with methylene blue and eosin and with Van Gieson's stain and Verhoeff's elastic tissue stain. The symptoms presented during life, as recorded in the case report, were compared with

the pathologic findings. This was the least satisfactory portion of the investigation, since the clinical findings had been recorded by different observers with varying degrees of care and accuracy, and often information on important points was missing.

Classification.—A surprisingly large number of different pathologic processes were found in the pulmonary vessels in the course of the investigation. They may be classified as follows (each type of lesion will be considered in turn, irrespective of what part of the pulmonary vascular bed is involved, though for the sake of clarity they are here classified by site as well as by pathologic type):

DISEASES OF THE ARTERIES

1. Arteriosclerosis: (*a*) secondary, (*b*) primary
2. "Endarteritis obliterans"
3. Proliferation of the elastica interna
4. Endothelial proliferation
5. Hypertrophy of the media
6. Fibrosis of the media
7. Syphilis of the pulmonary arteries
8. Ayerza's disease
9. Tubercle of the pulmonary arteries
10. Rheumatism of the pulmonary arteries
11. Acute septic arteritis.
12. Neoplasm
13. Thrombosis and embolism
14. Aneurysm

DISEASES OF THE ARTERIOLES AND VENULES

1. Sclerosis
2. Endothelial proliferation
3. Infections, acute and chronic
4. Neoplasm
5. Thrombosis

DISEASES OF THE VEINS

1. Sclerosis
2. Infections, acute and chronic
3. Neoplasm
4. Thrombosis

SECONDARY PULMONARY VASCULAR ARTERIOSCLEROSIS

Sclerosis of the pulmonary arteries is usually subdivided into primary and secondary types. In the primary type none of the conditions, such as mitral stenosis or chronic pulmonary disease, which are generally thought to cause a rise in the pulmonary arterial pressure, is present and there is an otherwise unexplained hypertrophy of the right ventricle. In secondary sclerosis one or more of the conditions that are thought to be capable of raising the pulmonary arterial pressure are present or, if they are absent, there is no hypertrophy of the right ventricle. Most of the cases of senile pulmonary arteriosclerosis fall into the group in which there is no obvious cause for a rise in the pulmonary arterial pressure but in which there is no hypertrophy of the right ventricle. No place has been found for this large group in previous definitions, or else the definitions have been so faulty that these cases should logically have been included in the category of primary sclerosis.

CLASSIFICATION OF THE CONDITIONS

Since chronic diseases of the heart and lung have usually been stated to be the chief causes of secondary sclerosis the 100 cases in the present series have been divided into eight groups according to the presence or absence of these factors:

1. The "no cause" group (31 cases), in which none of these factors was present though in 12 cases pleural adhesions were present, and in one of these one pleural cavity was obliterated, the other being normal.

2. The "pulmonary disease" group (29 cases), in which chronic disease of the lung was present: 16 cases of emphysema, 3 of emphysema with fibrosis of the lungs, 2 of bronchiectasis, 3 of fibrocaseous tuberculosis, 2 of tuberculosis with emphysema, 2 of chronic abscess of the lung and 1 of neoplasm.

3. The cardiac disease group (7 cases), in which cardiac disease alone was present: 5 cases of disease of the coronary artery with cardiac hypertrophy, 1 case of rheumatic mitral and aortic disease and 1 of hypertrophy of unknown origin in a boy aged 16 years.

4. The hypertension group (9 cases), in which essential hypertension or chronic glomerulonephritis with hypertension was present.

5. The "cardiac and pulmonary disease" group (13 cases), in which both chronic cardiac and chronic pulmonary disease were present: 5 cases of disease of the coronary artery with cardiac hypertrophy and emphysema, sometimes also with pulmonary fibrosis; 3 of rheumatic heart disease (including 1 case that was complicated by infective endocarditis), with emphysema or pulmonary fibrosis; 3 of syphilitic aortitis with pulmonary fibrosis (in 1 case with bronchiectasis and in another

case with fibrocaseous tuberculosis); 1 of aortic stenosis (? arteriosclerotic) with emphysema and pulmonary fibrosis, and 1 of pericarditis with emphysema.

6. "Cardiac disease and hypertension" group (3 cases) in which there was independent cardiac disease (sclerosis of the coronary artery with cardiac hypertrophy and in 2 cases occlusion of the coronary artery with myocardial infarction) in addition to hypertension.

7. "Cardiac and pulmonary disease and hypertension" group (3 cases), in which all 3 factors were present. In addition to hypertension in 1 case there was syphilitic aortitis and emphysema, and in 2 cases sclerosis of the coronary artery with emphysema.

8. "Pulmonary disease and hypertension" group (5 cases), in which there was chronic pulmonary disease (3 cases of emphysema, 1 case of emphysema with pulmonary fibrosis, and 1 of fibrocaseous tuberculosis with emphysema) as well as hypertension.

INCIDENCE

In the few systematic inquiries into pulmonary arteriosclerosis that have been made, estimates of its frequency have varied widely for three main reasons: 1. For some papers [h] the statistics were obtained from routine autopsy protocols, in which usually only extreme pulmonary vascular sclerosis is noted. It is rare in routine autopsies for the pulmonary vessels to be carefully examined, and unless specially looked for, most cases will be missed. Miller [203] found an incidence of pulmonary arteriosclerosis of 7.4 per cent in 800 routine autopsies and Moschowitz,[213] 6.5 per cent in 770 cases. Both these figures are much too low. 2. Sclerosis of the small vessels can be detected only microscopically, and even in the large vessels marked diffuse intimal thickening may easily be missed by the naked eye. Costa [63] noted sclerosis in the stem of the pulmonary artery macroscopically in only 8 per cent of 210 cases and microscopically in 65 per cent of the same cases. Not all authors have agreed as to what constitutes arteriosclerosis. Giroux [114] excluded cases in which there were only a few fatty patches or streaks in the intima, the rest of the intima appearing normally thin and translucent. But on microscopic study the normal-looking intima is often found to be considerably thickened. These changes undoubtedly represent mild or moderate grades of arteriosclerosis, and there is no logical reason for excluding them.

Of the 100 cases in the present series 59 were in males and 41 in females. Macroscopic evidence of sclerosis was present in 68 (41

(*h*) 203, 213.

males, or 70 per cent, and 27 females, or 66 per cent). The only available comparable statistics are those of Steinberg,[284] who on careful macroscopic examination of the pulmonary arteries in 500 unselected autopsies observed sclerosis in 65 per cent. In his series, as in the present one, males and females were affected in equal numbers.

In the present series, on microscopic examination, in only 3 cases (all in children under 10 years of age) were no sclerotic changes noted in any part of the pulmonary vascular bed. Thus, sclerotic changes (often slight) were seen in some part of the pulmonary vascular bed in 97 per cent of an unselected consecutive series of autopsies. This fact robs the observation of sclerotic changes in the pulmonary vessels of much of the significance that has heretofore been attributed to it. Sclerosis was observed as common in the pulmonary as in the systemic circulation (though less severe usually), and there is no reason to believe that it is more important. Indeed, since the lungs are less vulnerable than the heart or brain and since destruction of large portions of the lung may occur without endangering life, it is probably of less importance.

No comparable figures as to the frequency of pulmonary vascular sclerosis as observed on microscopic examination are available in the literature.

GROSS APPEARANCE

The macroscopic appearances in cases of secondary pulmonary arteriosclerosis differ from those of sclerosis of the systemic vessels only in usually being less severe.

(*a*) *Dilatation.*—The stem and branches of a sclerosed pulmonary artery are usually dilated.[1] In the present series in the 15 cases in adults in which no macroscopic evidence of sclerosis was found (slight microscopic sclerosis was present in all but 1 case) and in which there was none of the diseases thought to be capable of raising the pulmonary arterial pressure, the circumference of the stem of the pulmonary artery 2 cm. above the cusps ranged from 5.8 to 8.3 cm., except in 1 case, in which it was 9.3 cm., and that of the main branches at the hilus of the lung varied from 3.8 to 4.8 cm., except in one case, in which it was 5.1 cm. The pulmonary arteries have, therefore, been considered to be dilated if the circumference of the stem exceeded 8.5 cm. or if that of the main branches at the hilus exceeded 5 cm. Table 1 shows the distribution and severity of the dilatation in the 100 cases graded according to the severity of the sclerosis noted macroscopically. The manner in which the severity of the sclerosis was graded will be described presently. It is clear that in the present series the dilatation of the

(*i*) 78, 92, 114, 136, 160, 167, 174, 183, 186, 193, 204, 250, 273, 274, 308, 331.

TABLE 1.—*Incidence of Dilatation of the Pulmonary Arteries in Adults Over 20 with Pulmonary Vascular Sclerosis*

	Males														Females											
		Circumference of Stem, Cm.			Circumference at Hilus, Cm.			Dilatation of Stem		Dilatation at Hilus		Dilatation of Stem and at Hilus		Dilatation		Circumference of Stem, Cm.			Circumference at Hilus, Cm.			Dilatation of Stem		Dilatation at Hilus		Dilatation of Stem and at Hilus		Dilatation	
Degree of Sclerosis	No. of Cases	Minimum	Maximum	Average	Minimum	Maximum	Average	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Minimum	Maximum	Average	Minimum	Maximum	Average	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage	No. of Cases	Percentage
0	9	7.2	9.4	7.9	3.8	5.1	4.4	1	11	1	11	1	11	3	33	10	5.8	10.3	4.5	3.8	7.5	4.8	..	..	..	..	1	10	1	10
+	13	6.8	9.2	8.0	3.0	7.3	5.1	2	15	1	8	2	15	5	39	14	5.9	8.5	7.2	3.7	5.5	4.5	3	21	1	7	..	..	4	29
++	15	6.9	10.3	8.4	4.7	5.9	5.4	3	20	3	20	4	27	10	67	7	6.6	9.0	8.4	3.8	6.0	4.9	3	43	1	14	2	28	6	85
+++	10	6.8	10.2	8.1	4.7	7.5	5.5	..	..	2	20	4	40	6	60	4	7.3	8.9	8.2	5.1	7.0	5.8	..	..	2	50	2	50	4	100
++++	0	...	...	...	...	...	...	..	..	..	..	..	..	..	..	1	9.0	...	...	5.5	...	...	..	..	1	..	..	..	1	..

pulmonary artery was much commoner in cases of sclerosis, particularly of the severer grades, than in those in which sclerosis was not present. The greater frequency of dilatation in the males with no, or slight, sclerosis was perhaps due to the fact that the same upper limit for the normal was taken for both sexes, whereas the average circumference for normal women is distinctly less than that for normal men. There were relatively more cases of the higher grades of sclerosis in the more advanced age groups, and it is possible that the greater prevalence of dilatation in those groups may have been due to this; but the number of cases in which there was no sclerosis in the older age groups was too small for this factor to be controlled.

Dilatation may be the only macroscopic sign of pulmonary vascular sclerosis. In the case of a woman in whom the vessels were apparently normal, except that the circumference of the stem of the pulmonary artery was 9.3 cm., fairly marked sclerosis was seen microscopically. The same was true in two of Schreyer's cases.[274]

It is probable that during life the circumference of the pulmonary vessels is greater than at autopsy, and it is possible that during life the circumference of the normal vessels may be as great as that of those that are apparently dilated at autopsy. If this is so, the "dilatation" is really a measure of the lack of elasticity of the vessels. The post-mortem "dilatation" in either event indicates an abnormal condition of the vessels.

(*b*) *Atherosclerosis.*—Small, irregular, whitish or yellow patches or streaks elongated in the direction of the blood stream are present in the intima of the affected vessels. In the slighter grades they are not raised above the surface, but in severer cases they may be raised considerably. The patches are commonest and largest near the mouths of branches. Calcification is rare and is usually noted only on microscopic examination, but occasionally [262] it is seen macroscopically. Atheromatous ulcers are rare and have been reported only by Hornowski.[136] In the most severe cases the plaques may be almost confluent in some places. In the extrapulmonary and larger intrapulmonary arteries the intima between the patches often seems thickened and opaque, but in the smaller arteries, except in the most marked cases, it seems normally thin and translucent. In a few of the most severe cases in the present series the thickened intima looked wrinkled, owing, as shown microscopically, to the presence of deep furrows in the otherwise uniformly thickened intima. In a few cases the stem and extrapulmonary branches were thick and heavy, owing to thickening of the media. Usually in severe cases the smaller intrapulmonary branches were thickened and rigid, and their wide gaping mouths were unusually prominent on the cut surface of the lung.

In the present series the severity of the macroscopic changes has arbitrarily been graded from +, when there were only a few isolated fatty patches, to + + + +, when practically no normal intima could be found in any branch that could be opened up with fine scissors. The distribution of the cases according to the severity of the macroscopic sclerosis in males and females is shown in table 2. Though the incidence of sclerosis is approximately equal in the two sexes, there is a slight preponderance of the more severe grades of sclerosis in males. Steinberg,[284] who graded his cases similarly, graded 37 per cent of his cases +, 24 per cent + +, 10 per cent + + + and 3 per cent + + + +, figures which compare fairly closely with those in table 2.

(*c*) *Distribution of Sclerosis.*—The changes are least marked in the stem of the pulmonary artery and its extrapulmonary branches, a fact which accounts for the common underestimation of the frequency of

TABLE 2.—*Degree of Gross Vascular Sclerosis in Males and Females*

Degree of Sclerosis	Males		Females		Total Percentage
	Number	Percentage	Number	Percentage	
0	18	31	14	34	32
+	13	22	15	37	28
+ +	17	29	6	15	23
+ + +	11	19	5	12	16
+ + + +	..	..	1	2	1

pulmonary arteriosclerosis. Sclerosis in the stem is commonest just before the bifurcation and immediately above the cusps, which occasionally are involved at their commissures, so that the cusps may adhere slightly to each other and to the arterial wall. A similar but much more severe process causes arteriosclerotic aortic stenosis, but in the pulmonary artery the changes are minimal, and no case of arteriosclerotic stenosis of the pulmonary valve has been reported. The changes usually increase at the hilus of the lung. They sometimes reach their maximum in the main intrapulmonary branches and rapidly diminish in the smaller arteries, even in cases in which the microscope shows extensive lesions in the smallest vessels. In other cases the sclerosis extends into the smallest vessels that can be traced with the naked eye.

Laubry [158] said that in cases of chronic disease of the lung sclerosis is confined to the large branches, while in cases of heart disease all the branches down to the smallest that can be traced are involved. However, many cases of pulmonary disease have been reported in which the sclerosis extended to the finest traceable vessels,[j] and fewer cases have

(*j*) 92, 186, 193, 250, 262.

been reported in which there was sclerosis only of the large branches,[k] while in cases of heart disease sometimes the medium-sized vessels are said to be chiefly involved [252] and sometimes the large vessels [1] but usually all the branches down to the finest.[m]

Table 3 shows the distribution of macroscopic sclerosis in the present series in the various etiologic groups as defined previously. Macroscopic sclerosis of the large vessels alone was commoner than sclerosis of both large and small vessels, and there was no significant difference in the distribution in the various etiologic groups. In cases of congestive heart failure, however, the small vessels were more commonly involved. It should be stressed that the vessels here called small were all more than 1 mm. in external diameter and they were all histologically classed as "large elastic arteries." The distribution of the gross changes is not

TABLE 3.—*Distribution of Gross Sclerosis in the Pulmonary Arteries*

Etiologic Groups	Patients with Sclerosis in Large Arteries Only	Patients with Sclerosis in Large and Small Arteries
No case	10	3†
Pulmonary disease	18	6
Cardiac disease	3	2
Hypertension	5	..
Pulmonary and cardiac disease	8	3
Cardiac disease and hypertension	2	..
Pulmonary and cardiac disease and hypertension	1	1
Pulmonary disease and hypertension	3	2
Congestive heart failure*	8	6

* The cases of congestive heart failure are all included in one or the other of the eight etiologic groups.
† Including 1 patient with primary sclerosis.

necessarily related to the distribution of the microscopic changes in the small muscular arteries, arterioles and venules.

Table 4 shows that macroscopic sclerosis increased in frequency with age in both sexes. Of 30 patients under 40, 8 (27 per cent) showed sclerosis, while of 70 patients over 40, 60 (86 per cent) showed sclerosis. The influence of the factors thought capable of raising the pulmonary arterial pressure must be excluded before the effect of age can be evaluated. Table 5 shows that of the 31 patients in whom no such factor was present 16 were under and 15 over 40. Excluding 1 patient with primary pulmonary arteriosclerosis who was under 40, only 1 of the 15 patients under 40 (7 per cent) and 12 of the 15 over 40 (80 per cent) showed macroscopic sclerosis. Thus, the incidence of macroscopic pulmonary arteriosclerosis increased with the age of the patients even in the absence of factors commonly thought to raise the pulmonary

(*k*) 202, 204.
(*l*) 176, 335.
(*m*) 52, 78, 162, 273, 276, 306, 335.

arterial pressure. Ljungdahl [176] observed gross pulmonary arteriosclerosis in 50 per cent of 52 persons over 50 with no factor present which was thought likely to have raised the pulmonary arterial pressure. Others [n] have said that slight sclerosis is common in the aged, but no statistics have been given. Fischer [103] agreed, but attributed the increase to the presence of senile emphysema (which was excluded in the cases in the "no cause" group in the present series). Moschowitz [o] stated that decrescent pulmonary arteriosclerosis is rare until the patients are well on in senility. This conclusion was probably reached because no special search for pulmonary arteriosclerosis was made. Costa [63] said that although microscopic sclerosis of the stem of the pulmonary artery is almost always present in patients over 60, the gross changes are rare. However, the gross changes are always least in the stem of the pulmonary artery. Thus, nothing in the literature invalidates the

TABLE 4.—*Distribution of Gross Sclerosis According to Age and Sex*

	Males		Females	
Age, Years	No. of Patients	No. of Patients with Sclerosis	No. of Patients	No. of Patients with Sclerosis
0–9	2	0	3	0
10–19	9	1	..	..
20–29	3	2	2	1
30–39	5	3	6	1
40–49	10	6	3	2
50–59	14	14	9	6
60–69	12	12	8	7
70–79	4	3	8	8
80–89	..	..	2	2

conclusion that gross pulmonary arteriosclerosis is increasingly common with an increase in age, even in the absence of any evidence of a raised pulmonary arterial pressure.

Table 5 shows that in the presence of disease of the heart or lung, separately or together, the incidence of gross sclerosis is somewhat increased in patients under 40, but not significantly in those over 40, though after the age of 40 the severity of the sclerosis is increased.

MICROSCOPIC CHANGES

The smallest arteries that can be opened and examined macroscopically are from 1 to 2 mm. in diameter and are classed microscopically as large arteries. Macroscopic inspection gives no information about the small arteries, and even in the large vessels the microscope often reveals unsuspected lesions. Microscopic sclerosis may involve vessels of all sizes, from the stem of the pulmonary artery

(*n*) 150, 284, 295.
(*o*) 212, 213.

to the arterioles, and from the venules to the main veins. The appearances vary somewhat in different situations.

Method of Grading the Lesions.—It was felt that some numerical method of grading the lesions was desirable. It is obvious that any method must be rough and that no statistical accuracy can be claimed. The figures given in the following tables are intended merely as a rough indication of the differences in the severity of the lesions in the different groups of cases. In every case the severity of the lesions in each type of vessel (stem of the pulmonary artery, large elastic arteries, muscular arteries and so forth) was graded from 0 to ++++, according to the criteria given for each type of vessel.

TABLE 5.—*Distribution of Gross Pulmonary Arteriosclerosis According to Age and Etiologic Factor*

	Patients Aged 0 to 39 Years				Patients Aged 40 to 89 Years			
		Patients with Sclerosis				Patients with Sclerosis		
Etiologic Factor	No. of Patients	Number	Percentage	Average Degree of Sclerosis†	No. of Patients	Number	Percentage	Average Degree of Sclerosis†
No cause*	15	1	7	0.2+	15	12	80	1.3+
Pulmonary disease	6	3	50	0.7+	23	20	87	1.5+
Cardiac disease	2	1	..	2.0+	5	4	80	2.0+
Hypertension	3	1	..	0.3+	6	4	67	1.3+
Pulmonary and cardiac disease	3	1	..	0.3+	10	10	100	2.3+
Cardiac disease and hypertension	..	..	..	.....	3	2	67	1.0+
Pulmonary and cardiac disease and hypertension	..	..	..	.....	3	3	100	2.3+
Pulmonary disease and hypertension	..	..	..	.....	5	5	100	2.0+

* The patient with primary pulmonary vascular sclerosis is omitted from the "no cause" group of patients under 40.

† The average degree of sclerosis is obtained by adding together the pluses in each group and dividing by the number of cases in the group.

METHOD OF GRADING THE LESIONS

The thickness of the intima, either absolute or expressed as a percentage of the thickness of the vessel wall or of the vessel's external diameter, was the basis of classification. If in a given vessel there was a patch of sclerosis 0.2 mm. thick over one-fourth the circumference, the rest of the intima consisting of endothelium directly on the elastica interna, the "average thickness of the intima" for this vessel was taken as 0.2 divided by 4, or 0.05 mm. The "average intimal thickness" was obtained by adding the thickness of, for instance, twenty small muscular arteries and dividing by 20, to obtain the "average intimal thickness of the small muscular arteries." (Actually, for the small muscular arteries the intimal thickness was expressed as a percentage of the external diameter of the vessels, and it was these figures which were averaged, since obviously an intima 0.05 mm. thick is more important in a small than in a large artery.) The "average thickness of the intima of the small muscular arteries" for all the 16 cases in the "no cause" group in patients under 40 were then added together and divided by 16 to obtain the "average thickness of the intima" of the small muscular arteries in the "no cause"

group in patients under 40. Similarly, the average degree of the sclerosis in the small muscular arteries in the 16 cases in the "no cause" group in patients under 40 was obtained by adding together the plus signs given in each case for the degree of sclerosis of the small muscular arteries and dividing by 16. The same process was gone through for each type of vessel and for each of the etiologic subgroups. It must be stressed again that the resulting figures are useful only as a rough measure of the differences in the degree of sclerosis in the etiologic groups.

Stem of the Pulmonary Artery.—In children the intima consists of endothelium which lies directly on the elastica interna. In normal adults there may be an interposed layer of connective tissue up to 0.03 mm. thick. Sclerosis was considered to be present if the intima was more than 0.3 mm. thick. When it was from 0.03 to 0.1 mm. thick, the sclerosis was graded +; from 0.1 to 0.2 mm., + +, and from 0.2 to 0.3 mm., + + +. By using these criteria it was found that sclerosis was present in 54 of the 96 cases in which the stem was examined (56 per cent). Table 6 shows the distribution and severity of the changes in the various age, sex and etiologic groups. In some cases the changes were patchy or diffuse or there was slight general thickening with patches of greater thickening (fig. 2). The greatest thickness in any case in the present series was 0.299 mm., or 33 per cent of the thickness of the media. The thickened intima usually consisted of dense connective tissue (occasionally looser and more fibrillar) which stained pink or sometimes a muddy brown or yellow with Van Gieson's stain. A few round and spindle cells were present in all cases. In 2 cases, some of the patches contained small groups of 3 or 4 lymphocytes, and in 1 case, the much thickened intima contained many round cells. In 1 case one of the sclerotic patches was edematous and contained many fibroblasts, lymphocytes and large mononuclears. Fat was present only occasionally and only in the thickest patches. A few fat spaces were present in the depths of the lesion in 1 case, and in 2 cases there were linear groups of foam cells. Elastic tissue was usually present in the patches and was absent in only 9 cases. In these the sclerosis was often marked and the connective tissue in the intimal plaques was loose, fibrillar and cellular. The internal elastic lamina frays out and disappears at the edges of such patches. Occasionally a large sclerotic patch was divided by a fine elastic fibril into a superficial portion which stained yellow and a deep portion which stained pink with Van Gieson's stain. In a few cases the elastica interna beneath the thickest patches was frayed into fine fibrils, either fragmented or missing.

In no case did the intima show an internal longitudinal musculoelastic layer, but in 16 cases (all but 1 in patients over 40, and fairly evenly divided between the etiologic groups) the superficial 0.08 to 0.156 mm. of the media in places consisted of fine longitudinal elastic

TABLE 6.—*Relation of Histologic Changes in the Stem of the Pulmonary Artery to Age, Sex and Etiologic Factor*

		Males										Females									
		Patients with Sclerosis			Thickness of Intima, Mm.				Thickness of Media, Mm.			Patients with Sclerosis			Thickness of Intima, Mm.				Thickness of Media, Mm.		
Etiologic Factor	Age, Years	No. of Patients	Number	Percentage	Minimum	Maximum	Average	Average Degree of Sclerosis	Minimum	Maximum	Average	No. of Patients	Number	Percentage	Minimum	Maximum	Average	Average Degree of Sclerosis	Minimum	Maximum	Average
No cause	0–39	7	3	43	0	0.050	0.016	0.6+	0.647	1.573	0.830	7	1	14	0	0.266	0.030	0.3+	0.531	0.929	0.727
	40–89	11	5	45	0	0.117	0.033	0.6+	0.780	1.463	1.012	4	2	50	0	0.070	0.022	0.5+	0.553	1.115	0.766
Pulmonary disease	0–39	5	4	80	0	0.299	0.061	1.2+	0.481	1.212	0.822	1	0	..	.....	.....	.....	0	0.553	.....	.....
	40–89	10	7	70	0	0.098	0.038	0.7+	0.503	1.162	0.873	13	8	61	0	0.098	0.031	0.6+	0.531	1.328	0.870
Cardiac disease	0–39	1	0	..	.....	0.023	.....	0	.....	1.262	.....	1	1	..	.....	0.233	.....	3.0+	.....	1.162	.....
	40–89	4	2	50	0	0.051	0.026	0.5+	0.813	1.609	1.021	1	1	..	.....	0.219	.....	3.0+	.....	0.797	.....
Hypertension	0–39	1	1	..	0	0.059	.....	1.0+	.....	.....	.....	2	0	..	0	0.012	.....	0	.....	0.896	.....
	40–89	2	1	..	0.020	0.039	0.030	0.5+	0.913	1.594	1.254	4	1	25	0.016	0.033	0.024	0.3+	0.780	1.128	0.985
Pulmonary and cardiac disease	0–39	3	1	33	0	0.249	0.083	1.0+	0.614	1.245	0.960	..	..	..	.....	.....	.....	.....	.....	.....	.....
	40–89	8	7	88	0	0.266	0.087	1.4+	0.830	1.830	1.244	2	1	..	0.020	0.093	0.031	0.5+	.....	0.880	.....
Cardiac disease and hypertension	0–39	..	..	..	.....	.....	.....	.....	.....	.....	.....	..	..	..	.....	.....	.....	.....	.....	.....	.....
	40–89	2	2	..	0.043	0.133	0.113	1.5+	0.880	1.441	1.146	1	0	..	.....	0.016	.....	0	.....	1.278	.....
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	.....	.....	.....	.....	.....	.....	.....	..	..	..	.....	.....	.....	.....	.....	.....	.....
	40–89	2	7	..	0.016	0.059	0.032	0.5+	0.946	1.162	1.054	1	0	..	.....	0	.....	0	.....	0.631	.....
Pulmonary disease and hypertension	0–39	..	..	..	.....	.....	.....	.....	.....	.....	.....	..	..	..	.....	.....	.....	.....	.....	.....	.....
	40–89	2	2	..	0.059	0.166	0.113	1.5+	.....	1.196	.....	3	3	..	0.039	0.247	0.108	1.7+	.....	1.294	.....

fibers with a few coarser circular fibers embedded in dense connective tissue containing few or no muscle cells. Sclerosis was never found to involve that layer, so it is impossible to confirm the results of those writers [p] who have said that it begins there.

The only changes noted in the media were found to be as follows: 1. In aged patients there was often an increase in the connective tissue at the expense of the muscle and elastic tissue. 2. Beneath the large intimal plaques the media was often a little thinned. 3. There was a tendency to hypertrophy of the media in cases of heart failure in the "cardiac disease" group and in the "hypertension," "pulmonary and cardiac disease" and "pulmonary disease and hypertension" groups (table 6). Stains for fat were used in only a few cases, and the extension of fatty changes that have been said by some authors [q] to occur was not observed. Laubry [r] and others have said that in cases of pulmonary arteriosclerosis of whatever origin the medial elastic tissue is broken up and there is an increase in the amount of connective tissue. This description arouses the suspicion that the authors were not aware that in the normal pulmonary artery the elastic tissue is more broken up and the connective tissue more abundant than in the aorta.

The adventitia was usually normal, but in 5 cases there was a little focal or diffuse infiltration with lymphocytes, plasma cells and large mononuclears, and in 1 case the adventitia was edematous and infiltrated with lymphocytes, large mononuclears and a few polymorphonuclears. In 6 patients, all of whom were over 40, some of the vasa vasorum showed a thickened cellular intima.

Costa [63] said that in cases of pure mitral stenosis the intima is greatly thickened by dense connective tissue but no elastic tissue and little fat, while in cases of sclerosis due to other causes (even mitral stenosis if combined with regurgitation) there is a good deal of elastic tissue and fat. Others [s] have not confirmed this finding. Ljungdahl [176] found the changes in his patients with pulmonary and cardiac diseases to be similar to those in his senile patients, except that in the patients with cardiac disease the changes were more marked, and fat was present only when the disease was severe and not, as in some senile patients, with only slight intimal thickening. The analysis of the cases in the present series shows that there was no essential difference in the histologic picture in the various etiologic groups, though the changes were on the whole least severe in the "no cause" group and though there was a

(*p*) 92, 114, 296.
(*q*) 114, 176.
(*r*) 160, 165.
(*s*) 92, 176, 296.

tendency toward thickening of the media in the cases of cardiac disease either alone or complicated by pulmonary disease or hypertension.

Large Elastic Arteries.—Arteries more than 1 mm. in external diameter, in which the media consists of elastic laminae with little muscle and connective tissue, are included in this category. The thickness of the intima relative to the thickness of the wall exclusive of the adventitia (the limits of which it was sometimes difficult to define) was used in grading the degree of sclerosis. This is less inaccurate than a comparison with the external diameter of the arteries, since the large arteries are usually collapsed and not circular in cross-section. Nevertheless, an attempt to determine the presence of medial hypertrophy was

TABLE 7.—*Distribution of Sclerosis of the Large Elastic Arteries, According to Age and Sex*

	Males				Females			
		Patients with Sclerosis				Patients with Sclerosis		
Age, Years	No. of Patients	Number	Percentage	Average Degree of Sclerosis	No. of Patients	Number	Percentage	Average Degree of Sclerosis
0- 9	1	0	..	0	3	1	..	0.3+
10-19	9	7	78	1.6+	..	..	..	.....
20-29	3	3	..	1.3+	2	2	..	2.0+
30-39	4	4	..	2.0+	6	5	83	1.6+
40-49	10	10	100	1.8+	3	3	..	2.0+
50-59	14	14	100	2.0+	9	9	100	1.9+
60-69	12	11	91	1.9+	8	8	100	1.9+
70-79	4	4	..	2.0+	7	7	100	1.6+
80-89	..	..	..	.....	2	2	..	2.0+
Totals*	57	53	93	1.7+	40	37	93	1.7+

* Of the total number of 97 patients, 90 (93 per cent) showed sclerosis of the large elastic arteries (average degree of sclerosis, 1.7+). Of the 28 patients less than 40 years of age, 22 (78 per cent) showed sclerosis (average degree, 1.3+). Of the 69 patients over 40 years of age, 68 (98 per cent) showed sclerosis (average degree, 1.9+).

made by expressing the thickness of the media as a percentage of the external diameter of the vessel, the mean of the greatest and smallest diameters being taken for this purpose. The measurements of many large arteries in each case were averaged, as explained previously, in determining the average intimal and medial thickness in each case and in each group. The presence of any connective tissue between the endothelium and the elastica interna was interpreted as indicating the presence of sclerosis. If the average thickness of the intima was less than 20 per cent of that of the wall of the vessel, the sclerosis was graded + (individual sclerotic patches were as much as 40 per cent of the total thickness of the wall); from 20 to 30 per cent, + +; from 30 to 40 per cent, + + +, and over 40 per cent, + + + +.

Table 7 shows the age and sex distribution of the sclerotic changes. Sclerosis was present in 22 of 28 patients under 40 (78 per cent) and

in 68 of 69 over 40 (98 per cent). Thus sclerosis is common in youth and is almost constant and often severe in and after middle age.

Table 8 shows the incidence and severity of sclerosis in the various etiologic groups. In the "no cause" group, of the 16 patients under 40, 5 showed no sclerosis and 4 of these were under 20. In 4 of the remaining 11 patients there was only an occasional small patch of sclerosis in a few arteries. In 7 cases the sclerosis was more marked. The thickness of the media and the diameter of the lumen were normal. This table shows that in patients over 40 sclerosis was common even in

Fig. 5.—Photomicrograph showing a moderate degree of arteriosclerosis of a large elastic artery (× 17; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The media is thinned beneath the thickest portion of the sclerotic patch.

the absence of factors which are usually thought to raise the pulmonary arterial pressure (14 of 15 patients, or 93 per cent). The presence of such factors was associated with an increase in the frequency of sclerosis in patients under 40 and possibly with a slight increase in the severity of the lesions in patients over 40.

The changes resembled those in the stem and showed no essential differences in the various etiologic groups. There was slight or marked intimal thickening (fig. 5), involving part or all the circumference of few or many arteries. The intimal connective tissue was usually dense

TABLE 8.—*Distribution of Sclerosis in Large Elastic Arteries According to Age, Sex and Etiologic Factor*

Etiologic Factor	Age, Years	Males												Females											
			Patients with Sclerosis		Thickness of Intima*			Thickness of Media†			Diameter of Lumen†					Patients with Sclerosis			Thickness of Intima*			Thickness of Media†			Diameter of Lumen†		
		No. of Patients	Number	Percentage	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Degree of Sclerosis	No. of Patients	Number	Percentage	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Degree of Sclerosis
No cause	0-39	9	7	78	0	23	6	5	15	9	60	90	78	1.4+	7	4	57	0	37	12	5	13	9	67	90	76	1.0+
	40-89	10	9	90	0	36	16	4	15	8	68	89	80	1.6+	5	5	100	10	25	17	5	11	8	68	87	80	1.9+
Pulmonary disease	0-39	5	5	100	9	23	14	7	17	11	60	83	73	1.4+	1	1	..	..	1	..	..	12	..	..	66	..	1.0+
	40-89	10	10	100	5	58	16	2	13	7	67	90	81	1.9+	13	13	100	5	45	12	5	15	10	47	96	75	1.9+
Cardiac disease	0-39	1	1	..	..	30	..	..	8	..	..	81	..	3.0+	1	1	..	..	31	..	..	8	..	..	81	..	3.0+
	40-89	4	4	100	8	26	12	4	14	10	70	90	77	1.5+	1	1	..	..	29	..	..	7	..	..	82	..	2.0+
Hypertension	0-39	..	..	..	..	..	..	..	..	..	..	..	..	.....	2	2	..	6	13	9	8	12	10	..	78	..	1.0+
	40-89	2	2	..	10	25	18	..	10	..	71	72	72	1.5+	4	4	100	9	13	11	..	6	..	85	89	87	1.0+
Pulmonary and cardiac disease	0-39	3	2	67	0	25	9	6	8	7	77	83	80	1.0+	..	..	..	..	..	..	..	..	..	..	..	..	.....
	40-89	9	9	100	14	42	31	6	15	10	34	87	63	2.8+	2	2	..	14	31	23	..	8	..	78	84	81	2.0+
Cardiac disease and hypertension	0-39	..	..	..	..	..	..	..	..	..	..	..	..	.....	..	..	..	..	..	..	..	..	..	..	..	..	.....
	40-89	2	2	..	12	45	29	7	10	9	76	83	80	2.5+	1	1	..	..	15	..	..	9	..	..	79	..	1.0+
Pulmonary and cardiac disease and hypertension	0-39	..	..	..	..	..	..	..	..	..	..	..	..	.....	..	..	..	..	..	..	..	..	..	..	..	..	.....
	40-89	2	2	..	20	26	23	7	8	7	80	83	80	2.0+	1	1	..	..	27	..	..	6	..	..	84	..	2.0+
Pulmonary disease and hypertension	0-39	..	..	..	..	..	..	..	..	..	..	..	..	.....	..	..	..	..	..	..	..	..	..	..	..	..	.....
	40-89	2	2	..	20	26	23	12	13	13	72	76	74	2.0+	3	3	..	14	25	18	8	14	12	72	75	73	1.7+

* The thickness of the intima is expressed as a percentage of the thickness of the wall of the vessel exclusive of the adventitia.

† The thickness of the media and the diameter of the lumen are expressed as percentages of the external diameter of the vessel exclusive of the adventitia.

and hyaline, but in 10 cases some of the patches consisted of loose fibrillar connective tissue. This change occasionally was confined to part of a sclerotic patch. Usually the connective tissue contained a few round and spindle cells. In 6 cases some of the thickest patches contained small groups of lymphocytes. In 1 case there were numbers of large round cells. In 13 cases some of the patches showed foci of lymphocytes, large mononuclears and an occasional polymorphonuclear, and in 1 case these were so dense as to suggest inflammatory infiltration. In 2 cases in which there was acute arteritis due to the presence of septic emboli, there were many polymorphonuclears in the intimal patches. Red blood cells, enmeshed in a delicate reticulum, were present in a few patches in 1 case. The intimal plaques were infiltrated with tumor cells in 1 case of mediastinal tumor. Smooth muscle cells, chiefly longitudinal, were present in the thickest intimal patches in 8 cases. These cells were sometimes numerous but were usually scattered and did not form a definite compact layer in the thickened intima. Fat was present within groups of large foam cells in 29 cases. The foam cells were often arranged in rows and usually were present only in the thickest patches, though in some arteries in one case a single row of foam cells, embedded in a minimal amount of connective tissue, alone separated the endothelium from the elastica interna. In 7 cases spaces from which fat had been dissolved were present in the thickened intima. Fat seemed to be present in the intimal plaques rather more commonly in cases of pulmonary disease, either alone or combined with heart disease, than in the other groups.

In 1 case in which the lumen contained an organizing thrombus, capillaries were present in the thickened intima.

In 13 cases there was no elastic tissue except the elastica interna in the sclerotic patches. In most cases there were few or many fine, rather poorly staining elastic fibrils in the depths of the patches. Usually these were irregularly arranged, but in 15 cases in some of the patches the fibrils ran parallel to, and seemed to be split off from, the elastica interna. In 2 cases in some patches the elastica interna split to enclose a wide oval of connective tissue full of fine elastic fibrils. In 8 cases some of the thickest sclerotic patches were subdivided by a fine elastic fibril (in 1 case by a narrow sheaf of fine fibrils) into a superficial portion which stained yellow and a deep portion which stained pink with Van Gieson's stain. The elastica interna was usually a coarse, densely staining band continuous around the whole circumference of the vessel, but in 18 cases in some of the patches it either frayed out into fibrils or became fragmented, and beneath some of the thicker patches it disappeared altogether. In 1 case the medial elastic laminae beneath a thick patch also disappeared.

These intimal changes in themselves rarely caused marked narrowing of the lumen, though in some cases the lumen was narrowed or obliterated by thrombi.

The media was often thinned beneath the thickest patches. The average thickness of the media was 8 per cent of the external diameter of the vessel excluding the adventitia, in the cases of the "no cause" group patients over 40 and in the cases of the "cardiac disease" group patients under 40. This is less than the normal average (9.8 per cent), though within the normal range. In both cases in the latter group congestive heart failure was present, so that there is no evidence that congestive failure (presumably associated with a high pulmonary arterial pressure) causes medial hypertrophy in the large elastic arteries. There was no tendency for the media to be thickened except possibly in the "pulmonary disease and hypertension" group, and there the numbers were too small for statistical accuracy. In 1 case some longitudinally arranged muscle was present in patches. In 3 patients over 40 there was rather more connective tissue than usual in the outer part of the media. In 1 patient under 40 in the "pulmonary disease" group the superficial 0.06 mm. of the media of one artery in a long stretch consisted of dense connective tissue with no muscle or elastic tissue. In 1 patient under 40 in the "hypertension" group one artery in the superficial half of its media showed no elastic laminae but only irregular elastic fibrils, a great deal of connective tissue and little muscle, chiefly longitudinally arranged.

In the cases reported in the literature, also, there were no distinctive variations in the histologic appearances of the sclerosis according to the etiologic factor present, and the changes reported were similar to those just described, though usually no detailed description was given.[t] In many cases changes were also described in the media,[u] the commonest being the extension of fatty degeneration, sometimes with a little calcification, into its superficial part. This was never observed in the present series. An excess of fibrous tissue was noted in the media more commonly than in the present series. In some cases there was a proliferation of the medial elastic tissue, sometimes resulting in thickening of the media.[308] Wiesel[v] described focal edema of the media, followed by fibrosis and sometimes calcification, as a sequel of acute infections. In the present series the medial changes were much less conspicuous than they seemed to be in the cases reported in the literature.

(*t*) 64, 78, 94, 102, 114, 136, 150, 160, 161, 165, 174, 176, 186, 193, 250, 276, 284, 295, 296, 306, 331.

(*u*) 64, 94, 102, 136, 160, 161, 165, 174, 176, 250, 284, 295, 307, 308, 324, 325.

(*v*) 324, 325.

The adventitia only occasionally showed abnormalities in the present series. In 2 cases of acute septic arteritis due to the presence of septic emboli in the lumen the adventitia was infiltrated with polymorphonuclears. In 2 cases (in 1 of which the lumen contained a thrombus) there was focal round cell infiltration of the adventitia. In 1 case opposite a parietal thrombus in the lumen the adventitia showed dilated capillaries, endarteritis obliterans of the vasa vasorum and a great deal of infiltration with lymphocytes and large mononuclears. The vasa vasorum showed a thick cellular intima in 3 cases, all in patients over 40. It was invaded by tumor cells in 1 case of mediastinal tumor and by caseous tuberculosis in another case.

TABLE 9.—*Distribution of Sclerosis in Small Muscular Arteries According to Age and Sex*

	Males				Females			
		Patients with Sclerosis				Patients with Sclerosis		
Age, Years	No. of Patients	Number	Percentage	Average Degree of Sclerosis	No. of Patients	Number	Percentage	Average Degree of Sclerosis
0–9	2	1	..	1.0+	3	1	..	0.7+
10–19	9	6	67	1.2+	..	..	..	.....
20–29	3	3	..	2.3+	2	1	..	1.0+
30–39	5	4	80	1.0+	6	6	100	1.7+
40–49	10	10	100	1.8+	3	3	..	2.3+
50–59	14	13	93	2.0+	9	8	89	1.6+
60–69	12	12	100	2.5+	8	8	100	2.5+
70–79	4	4	..	1.8+	8	8	100	2.8+
80–89	..	..	..	.....	2	2	..	2.5+
Totals*	59	53	90	1.7+	41	37	90	2.0+

* Of the 100 patients, 90 (90 per cent) showed sclerosis of the small muscular arteries (average degree, 1.8+). Of the 30 patients less than 40 years of age 23 (73 per cent) showed sclerosis (average degree, 1.3+). Of the 70 patients over 40 years of age, 68 (97 per cent) showed sclerosis (average degree, 2.2+).

Small Muscular Arteries.—Less attention has been paid in the literature to the small muscular arteries, and it is frequently difficult to be sure that the muscular arteries are meant when the authors speak of "small arteries," since the accompanying illustrations often show arteries of the elastic type. Tables 9 and 10 show the distribution of sclerosis of the muscular arteries in the present series according to age, sex and etiologic factors. Normally the intima consists of endothelium directly on the elastica interna, and sclerosis was considered to be present if any connective tissue intervened. When the average thickness of the intima was less than 2 per cent of the external diameter of the vessel excluding the adventitia the sclerosis was graded +, when the intimal thickness was from 2 to 10 per cent of the diameter, + +; when it was from 10 to 20 per cent, + + + and when it was over 20 per cent, + + + +. Sclerosis of the muscular arteries was present in 90 per cent of cases and was evenly distributed between the sexes, though slightly more

TABLE 10.—*Distribution of Sclerosis of Small Muscular Arteries According to Age, Sex and Etiologic Factor* *

Etiologic Factor	Age, Years	Males							Females						
		No. of Patients	Patients with Sclerosis		Thickness of Intima	Thickness of Media	Diameter of Lumen	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Intima	Thickness of Media	Diameter of Lumen	Average Degree of Sclerosis
			Number	Percentage						Number	Percentage				
No cause	0–39	9	5	55	1 (0–2)	10 (4–18)	79 (65–87)	0.7+	7	4	57	2 (0–8)	9 (6–13)	77 (68–86)	0.7+
	40–89	10	10	100	8 (1–17)	10 (8–16)	64 (42–86)	1.5+	5	4	80	2 (0–4)	9 (6–13)	75 (56–89)	1.2+
Pulmonary disease	0–39	5	5	100	7 (1–16)	13 (8–20)	64 (58–78)	1.8+	1	1	..	6	14	58	2.0+
	40–89	10	10	100	7 (1–14)	10 (6–15)	68 (51–80)	2.1+	13	13	100	11 (1–17)	11 (7–17)	54 (22–77)	2.4+
Cardiac disease	0–39	1	1	..	7	12	66	2.0+	1	1	..	6	11	67	2.0+
	40–89	4	4	100	6 (1–9)	9 (7–11)	72 (61–79)	1.8+	1	1	..	2	8	79	1.0+
Hypertension	0–39	1	0	..	0	9	82	0	2	2	..	8 (5–10)	13 (10–16)	58 (57–60)	2.0+
	40–89	2	2	..	7 (6–8)	9 (8–9)	68 (60–75)	2.0+	4	4	100	8 (2–12)	10 (9–11)	62 (55–69)	2.0+
Pulmonary and cardiac disease	0–39	3	3	..	4 (1–7)	13 (12–13)	73 (71–75)	1.7+	..	..	..	..	..	..	.....
	40–89	8	7	89	7 (0–11)	11 (8–15)	56 (39–76)	2.3+	2	2	..	12 (12–12)	13 (11–19)	49 (47–53)	3.0+
Cardiac disease and hypertension	0–39	..	..	..	..	..	..	.....	..	..	..	..	..	..	.....
	40–89	2	2	..	4 (2–7)	9 (7–10)	78 (73–83)	1.5+	1	1	..	7	4	77	2.0+
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	..	..	..	.....	..	..	..	..	..	..	.....
	40–89	2	2	..	6 (2–10)	9 (7–11)	72 (62–82)	2.0+	1	1	..	2	7	82	1.0+
Pulmonary disease and hypertension	0–39	..	..	..	..	..	..	.....	..	..	..	..	..	..	.....
	40–89	2	2	..	12 (10–14)	16 (13–19)	56 (53–59)	3.0+	3	3	..	12 (11–12)	9 (7–10)	60 (57–62)	3.0+

* All measurements are expressed as percentages of the external diameter of the vessel exclusive of the adventitia. The first figure in the column represents the average percentage and the figures in the parentheses represent the extremes.

severe in the females. It was present in 22 of 30 patients under 40 (73 per cent) and was practically constant in those over 40 (68 of 70, or 97 per cent). It was also more severe in patients over 40. Table 10 shows the incidence and severity of the sclerosis in the various etiologic groups. Sclerosis is least frequent and least severe in the "no cause" group in patients under 40. Only 9 of the 16 patients showed sclerosis, and with the exception of the case of primary sclerosis and 1 other case in which it was marked, the sclerosis was slight and patchy and involved only a few arteries in each case. Slight sclerosis of the small pulmonary arteries is thus not uncommonly present in young persons in whom there is no evidence of a raised pulmonary arterial pressure during life, a point which appears not to have been previously appreciated. Of the 15 patients over 40 in the "no cause" group 14, or 93 per cent, showed sclerosis, though in all but 1 patient some arteries were normal and in 7 patients there was only slight patchy sclerosis of a few arteries. In 6 patients the lumen of many arteries was narrowed by the intimal thickening. Thus, even in the absence of factors thought to raise the pulmonary arterial pressure, sclerosis of the small muscular arteries is almost constant in patients over 40 and may sometimes be marked. Ljungdahl,[176] who is the only author who has described systematic examination of the small arteries in elderly persons in the absence of factors likely to raise the pulmonary arterial pressure, stated that sclerosis is common though less marked than in the larger arteries.

In the "pulmonary disease" group all the patients under 40 showed sclerosis, though in 3 only a few arteries showed a few small patches. In the remaining patients many arteries showed marked patchy or diffuse intimal thickening, often with narrowing of the lumen. The 23 patients over 40 showed sclerosis, though in 4 only a few arteries showed small patches. In 13 patients practically every artery showed intimal thickening, sometimes with narrowing of the lumen. In the remaining 6 patients there was an intermediate degree of sclerosis.

In the "cardiac disease" group both patients under 40 showed moderate sclerosis affecting many but not all the vessels. All the patients over 40 showed slight to moderate sclerosis. In all cases most of the small arteries were normal, but in 1 case the lumen of some vessels was narrowed by intimal thickening.

In the "hypertension" group sclerosis was present in 2 of the 3 patients under 40, in both of whom many arteries were normal. In all the patients over 40 sclerosis was present. Many arteries were normal and some had lumens narrowed by marked intimal thickening.

All the patients in the "pulmonary and cardiac disease" group showed moderate to marked sclerosis. In 3 the lumen of most vessels was much narrowed by intimal thickening. In the "cardiac disease and hypertension" and "pulmonary and cardiac disease and hypertension"

groups all the patients showed slight to moderate sclerosis. In the "pulmonary disease and hypertension" group all the patients showed marked sclerosis with narrowing of the lumen.

Thus, the observations indicate that sclerosis of the small muscular arteries is almost constant (though sometimes in only a few vessels) in patients over 40, irrespective of the presence or absence of chronic pulmonary or cardiac disease, but that the frequency of sclerosis in those under 40 and its severity in those over 40 are somewhat greater

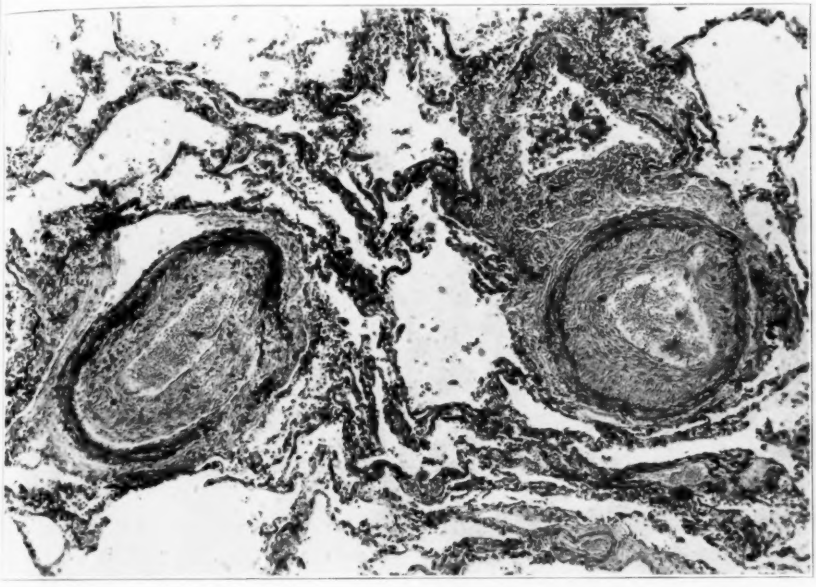

Fig. 6.—Photomicrograph showing sclerosis of small muscular arteries (× 192; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is marked intimal thickening with narrowing of the lumen in two small muscular arteries.

in the presence of chronic cardiac or pulmonary disease, separately or together.

The histologic changes (fig. 6) were in most respects similar to those in the large arteries and show no constant differences in the various groups. Normally the intima consists of endothelium directly on the elastica interna. The presence of any intervening connective tissue was taken to indicate the presence of sclerosis. The intimal thickening was at times slight and patchy, involving only a small portion of the circumference of the vessel, and at times there was marked thickening of

the intima all around the circumference of the vessel with marked narrowing of the lumen. The connective tissue was usually dense; it stained pink or yellowish with Van Gieson's stain and contained a few round or oval cells. In 4 cases the connective tissue of some of the patches was loose, fibrillar and cellular. In 1 case the intima of some of the larger muscular arteries showed foci of lymphocytes, large mononuclears and a few polymorphonuclears. In 1 case in which there was a chronic pulmonary abscess some of the vessels near the abscess showed dense infiltration of the intima with lymphocytes and large mononuclears. Polymorphonuclears were present in the thickened intima of one artery the lumen of which contained a septic embolus. In two cases the thickened intima was infiltrated with tumor cells. Fat was less common than in the large arteries, as is the case with sclerosis of the systemic vessels,[26] but it was present in foam cells in 2 cases and free in the thickened intima in 3 cases, in each case only in the larger of the muscular arteries. Elastic tissue was less abundant than in the large elastic arteries. There was a little poorly staining elastic tissue in some of the sclerotic patches in 20 cases, and in 7 cases it ran parallel to, and appeared to be split from, the elastica interna. In 1 case some of the thickest sclerotic patches were divided by a single elastic fibril into a superficial layer which stained yellowish and a deep layer which stained pink with Van Gieson's stain. In many cases the elastica interna was fragmented or missing beneath some of the thickest patches.

The media was often somewhat thinned beneath the thickest sclerotic patches. It showed in many cases other changes (fibrosis, inflammatory round cell infiltration and invasion by neoplasm and tuberculosis), to be described in the appropriate sections. The adventitia also showed similar changes.

Thus, the character of the changes was on the whole similar to that in the larger vessels and to that in small systemic muscular arteries and did not differ with the etiologic factor.

Arterioles and Venules.—These can be distinguished only if seen joining an artery or vein. Normally they consist of endothelial tubes, around which single, or occasionally double, elastic fibers are wound spirally. The presence of any connective tissue between the endothelium and the elastic fiber is abnormal. If the thickness of the vessel wall was less than 10 per cent of the external diameter, the sclerosis was graded +; if from 10 to 15 per cent, ++; if from 15 to 25 per cent, +++, and if over 25 per cent, ++++. Table 11 shows that sclerosis was present in 93 of 99 cases (94 per cent) and was equally common in males and females. It was present in 25 of 30 patients (83 per cent) under 40 and in 68 of 69 patients (98 per cent) over 40. Four of the 6 patients without sclerosis were children under

10 years of age. Table 12 shows that sclerosis of the arterioles and venules was almost constant in patients over 40 even in the absence of factors thought to raise the pulmonary arterial pressure, and it was common even in patients under 40. When cardiac or pulmonary disease or hypertension or any combination of these was present, the frequency and severity of sclerosis in patients under 40 were increased, but there was no significant increase either in the frequency or in the severity of sclerosis in patients over 40.

The sclerosis, when present, usually was more widespread than in the case of the larger vessels and involved most or all the arterioles and venules. Occasionally the change was patchy, but usually the whole

TABLE 11.—*Distribution of Sclerosis of the Arterioles and Venules According to Age and Sex*

	Males				Females			
		Patients with Sclerosis				Patients with Sclerosis		
Age, Years	No. of Patients	Number	Percentage	Average Degree of Sclerosis	No. of Patients	Number	Percentage	Average Degree of Sclerosis
0- 9	2	1	..	1.5+	3	0	..	0
10-19	9	8	89	1.4+	..	..	..	.....
20-29	3	3	..	3.7+	2	2	..	2.0+
30-39	5	5	100	2.0+	6	6	100	2.0+
40-49	10	10	100	2.0+	3	3	..	2.0+
50-59	14	13	93	2.0+	8	8	100	2.0+
60-69	12	12	100	2.7+	8	8	100	2.8+
70-79	4	4	..	2.5+	8	8	100	2.6+
80-89	..	..	..	.....	2	2	..	2.5+
Totals*	59	56	95	2.1+	40	37	93	2.2+

* Of the 99 patients 93 (94 per cent) showed sclerosis of the arterioles and venules (average degree, 2.1+). Of the 30 patients less than 40 years of age 25 (83 per cent) showed sclerosis (average degree, 1.8+). Of the 69 patients over 40 years of age 68 (98 per cent) showed sclerosis (average degree, 2.3+).

circumference of the vessel was involved (fig. 7). Between the endothelium and the elastic fiber there was a layer of connective tissue, usually dense and almost acellular, which stains pink or occasionally brownish or yellowish with Van Gieson's stain. In 2 cases the vessels near a chronic pulmonary abscess and a patch of fibrocaseous tuberculosis, respectively, showed thickening of their walls by looser connective tissue which contained many lymphocytes and fibroblasts. In several cases a few round cells lay in lacunae hollowed out between the connective tissue and the elastic fiber. In 2 cases the thickened wall of the vessel was infiltrated with tumor cells. The endothelium of many vessels was swollen in 2 cases and it was proliferated in a case of primary sclerosis in a boy of 11 in a few vessels, where the change had spread from the small muscular arteries, and in 1 other case near pyemic abscesses of the lung.

TABLE 12.—*Distribution of Sclerosis of the Arterioles and Venules According to Age, Sex and Etiologic Factor* *

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis
			Number	Percentage				Number	Percentage		
No cause	0-39	9	7	78	7 (2-15)	0.9+	7	5	72	11 (3-24)	1.2+
	40-89	10	10	100	17 (8-29)	2.3+	5	5	100	14 (8-19)	2.0+
Pulmonary disease	0-39	5	5	100	22 (4-32)	3.4+	1	0	..	6	0
	40-89	10	10	100	15 (5-26)	2.2+	13	13	100	17 (7-34)	2.5+
Cardiac disease	0-39	1	1	..	24	3.0+	1	1	..	21	3.0+
	40-89	4	4	..	13 (8-16)	1.5+	1	1	..	15	2.0+
Hypertension	0-39	1	1	..	15	2.0+	2	2	..	16 (11-17)	2.5+
	40-89	2	2	..	14 (10-17)	2.5+	4	4	..	19 (12-27)	3.0+
Pulmonary and cardiac disease	0-39	3	3	..	21 (18-24)	3.0+	..	..	..	..	.....
	40-89	8	7	88	17 (5-28)	2.3+	2	2	..	11 (10-12)	2.0+
Cardiac disease and hypertension	0-39	..	..	..	..	.....	..	..	..	..	.....
	40-89	2	2	..	15 (10-19)	2.0+	1	1	..	22	3.0+
Pulmonary and cardiac disease and hypertension	0-39	..	..	..	..	.....	..	..	..	..	.....
	40-89	2	2	..	13 (11-15)	2.0+	1	1	..	17	3.0+
Pulmonary disease and hypertension	0-39	..	..	..	..	.....	..	..	..	..	.....
	40-89	2	2	..	14 (10-18)	2.0+	3	3	..	21 (15-26)	3.0+

* The thickness of the wall of the vessel is expressed as a percentage of the total external diameter of the vessel. When measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.

Though the changes were usually widely and evenly spread throughout the lungs, in 1 case of fibrocaseous tuberculosis and in 1 case in which there were secondary deposits of growth in the lungs, the vessels near the lesions were greatly thickened, while those elsewhere were mostly normal.

Capillaries.—The capillaries showed no important changes except dilatation and engorgement in cases of congestive heart failure. These changes are of great importance in the production of the symptoms of

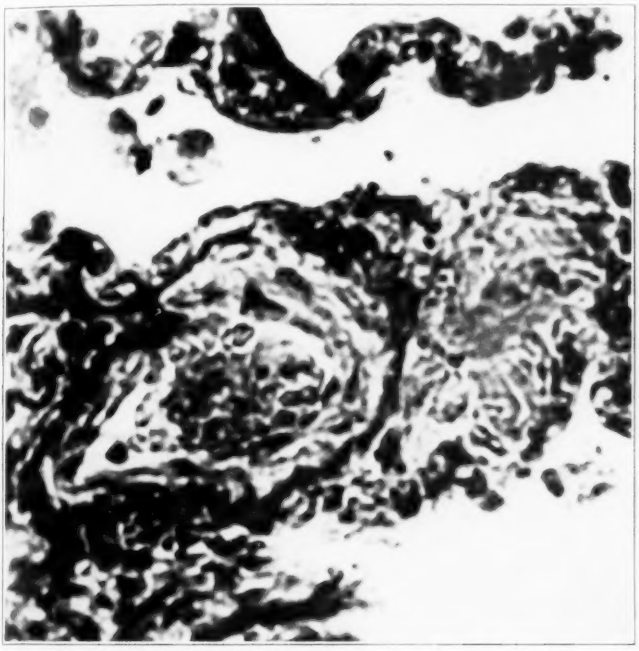

Fig. 7.—Photomicrograph showing sclerosis of an arteriole or venule (× 675; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is fairly marked thickening of the connective tissue within a single elastic fiber. The lumen is narrowed.

heart failure. Moschowitz [w] regarded them as part of an "arteriocapillary fibrosis" similar to that described in the systemic circulation by Gull and Sutton.

Small Veins.—Little attention has been paid in the literature to sclerosis of the pulmonary veins. Benda [27] observed only 1 case of sclerosis of the pulmonary veins, that of a woman of 28 with chronic

(*w*) 212, 213, 214.

nephritis and nephrosis; the main pulmonary veins showed intimal thickening with deposition of fat. Moschowitz [213] said that in cases of mitral stenosis sclerosis of the pulmonary veins is almost as common as sclerosis of the arteries. Prevot [242] observed no gross changes in the pulmonary veins in 60 cases but marked microscopic changes in 8 and moderate changes in 30. The changes were usually not so severe as in the arteries. There were fatty degeneration of the elastica interna and of the medial elastic tissue and thickening of the intima, with much deposition of fat either in foam cells or free in the connective tissue. The elastica interna often split as it approached the sclerotic patch. Brüning [48] frequently noted sclerosis of the pulmonary veins in his patients, though it was not so common or severe as in the arteries. It was most marked in patients with congestive heart failure, but was not confined to them. Zinsser [335] noted patchy intimal thickening with fatty change in only 1 of 9 cases of mitral stenosis. Ljungdahl [176] found gross changes in 17 of 36 cases of cardiac disease. Microscopic changes in the small veins were much slighter and less common. There were no changes in any of 45 patients with chronic pulmonary disease. In this he agreed with Moschowitz.[213] Rosenthal [256] observed circumscribed intimal thickening in many small veins in 2 of his 3 patients with pulmonary vascular sclerosis and pneumonoconiosis. Thus, in the few cases in which sclerosis of the pulmonary veins has been described, it was found chiefly in the large veins and was less common and slighter in the small veins.

Veins less than 1 mm. in external diameter are considered in this section. Up to a diameter of 0.25 mm. the veins have the same structure as the venules and consist of an endothelial tube around which a single elastic fiber is wound. When the diameter is over 0.25 mm., there are two or more elastic fibers with a little connective tissue and an occasional muscle cell. The normal thickness of the wall is from 2 to 7 per cent of the external diameter (average, 4 per cent). The occurrence of any connective tissue between the endothelium and the elasticofibromuscular layer representing the media was considered as evidence of sclerosis. When the average thickness of the wall of the vein was less than 10 per cent of the external diameter the sclerosis was graded +; between 10 and 15 per cent, + +; between 15 and 25 per cent, + + +, and over 25 per cent, + + + +.

Table 13 shows that sclerosis of the small veins was present in 90 of 99 patients (91 per cent) and was evenly distributed between the sexes. It was present in 22 of 29 patients under 40 (76 per cent) and in 68 of 70 patients over 40 (97 per cent). Table 14 shows that even in the absence of factors thought to raise the pulmonary arterial pressure, sclerosis of the small veins was constant in patients over 40. The presence of cardiac or pulmonary disease, alone or together, was asso-

ciated with an increase in the incidence of sclerosis in patients under 40 and with an increase in its severity in patients over 40. That the frequency and severity of sclerosis of the small pulmonary veins were increased in cases of pulmonary disease (contrary to the findings of Moschowitz and Ljungdahl) is noteworthy, since any obstruction to the pulmonary circulation is in the capillaries and the pressure in the veins might be expected to be low rather than high.

The changes consisted in the appearance of a layer of connective tissue between the endothelium and the medial elastic tissue. This was sometimes all around the circumference and sometimes present only in patches. In the affected patients most of the small veins (less than 0.25 mm. in diameter) are involved, while the larger veins, with a more

TABLE 13.—*Distribution of Sclerosis of Small Veins According to Age and Sex*

	Males				Females			
		Patients with Sclerosis				Patients with Sclerosis		
Age, Years	No. of Patients	Number	Percentage	Average Degree of Sclerosis	No. of Patients	Number	Percentage	Average Degree of Sclerosis
0–9	2	1	..	1.0+	3	0	..	0
10–19	9	7	78	1.7+	..	..	..	.....
20–29	3	3	..	2.3+	1	1	..	4.0+
30–39	5	5	100	1.2+	6	5	83	1.7+
40–49	10	9	90	1.8+	3	3	..	2.3+
50–59	14	13	93	1.7+	9	9	100	2.2+
60–69	12	12	100	2.2+	8	8	100	2.4+
70–79	4	4	..	2.5+	8	8	100	2.3+
80–89	..	..	..	.....	2	2	..	2.5+
Totals*	59	54	92	1.8+	40	36	90	1.9+

* Of the total number of 99 patients, 90 (91 per cent) showed sclerosis of the small veins (average degree, 1.9+). Of the 29 patients less than 40 years of age, 22 (76 per cent) showed sclerosis (average degree, 1.6+). Of the 70 patients over 40 years of age, 68 (97 per cent) showed sclerosis (average degree, 2.1+).

definite media, show less severe changes and sometimes many of them are normal. This was so in the cases in the "pulmonary disease" group, though in only 2 of the 23 patients over 40 were the larger veins entirely normal. In some cases the thickening of the intima was great enough to cause narrowing of the lumen, and in 1 case of healed pulmonary tuberculosis many of the small veins in the scarred areas were completely obliterated by an overgrowth of connective tissue. In 4 other cases in patients with fibrocaseous tuberculosis or chronic pulmonary abscess the changes in the veins were practically confined to the neighborhood of the pulmonary lesions.

The thickened intima usually consisted of dense, almost hyaline connective tissue which stained pink or occasionally yellowish or brownish with Van Gieson's stain and which was almost acellular. In 9 cases the veins that were near chronic or acute pulmonary abscesses

TABLE 14.—*Distribution of Sclerosis of Small Veins According to Age, Sex and Etiologic Factor* *

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis
			Number	Percentage				Number	Percentage		
No cause	0–39	9	6	67	7 (2–10)	0.7+	6	4	67	8 (3–20)	1.0+
	40–89	10	10	100	12 (4–19)	1.5+	5	5	100	14 (6–23)	1.8+
Pulmonary disease	0–39	5	5	100	22 (10–28)	2.8+	1	0	..	7	0
	40–89	10	10	100	15 (7–25)	2.0+	13	13	100	22 (8–36)	2.5+
Cardiac disease	0–39	1	1	..	26	4.0+	1	1	..	28	4.0+
	40–89	4	3	..	10 (3–20)	1.2+	1	1	..	29	4.0+
Hypertension	0–39	1	1	..	8	1.0+	2	1	..	21 (6–36)	2.0+
	40–89	2	2	..	12 (8–15)	1.5+	4	4	..	12 (11–14)	2.0+
Pulmonary and cardiac disease	0–39	3	3	..	18 (10–25)	2.0+	..	..	..	..	.....
	40–89	8	7	88	17 (3–29)	2.0+	2	2	..	21 (13–29)	3.0+
Cardiac disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	2	2	..	16 (7–25)	2.0+	1	1	..	15	2.0+
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	2	2	..	25 (15–35)	3.0+	1	1	..	8	1.0+
Pulmonary disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	2	2	..	30 (21–40)	3.5+	3	3	..	16 (14–18)	2.3+

* The thickness of the wall of the vessel is expressed as a percentage of the total external diameter. Where measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.

or patches of active pulmonary tuberculosis were narrowed by a thick layer of loose connective tissue containing many lymphocytes, large mononuclears and fibroblasts. In 1 case the walls of the thickened veins near a chronic pulmonary abscess contained many polymorphonuclears. In 4 cases the walls of some small veins were infiltrated by tumor cells. In 2 cases the thickened intima contained a few endothelium-lined lumens. In 6 cases the thickened intima contained a little fine irregular elastic tissue and some of the thickened patches were divided into superficial and deep layers by an elastic fiber.

In 3 cases, the media near chronic pulmonary abscesses or active foci of tuberculosis showed infiltration with lymphocytes, large

TABLE 15.—*Distribution of Sclerosis of Large Intrapulmonary Veins According to Age and Sex*

	Males				Females			
		Patients with Sclerosis				Patients with Sclerosis		
Age, Years	No. of Patients	Number	Percentage	Average Degree of Sclerosis	No. of Patients	Number	Percentage	Average Degree of Sclerosis
0–9	1	0	..	0	2	0	..	0
10-19	8	2	25	0.8+	..	..	..	.....
20-29	3	1	..	0.3+	2	1	..	2.0+
30-39	4	2	..	1.0+	5	2	40	0.4+
40-49	7	3	43	0.9+	3	2	..	0.7+
50-59	13	8	62	1.0+	7	2	29	0.3+
60-69	12	9	75	1.0+	8	6	75	1.3+
70-79	3	1	..	0.3+	7	5	71	1.0+
80-89	..	..	..	.....	2	1	..	0.5+
Totals*	51	26	52	0.9+	36	19	53	0.8+

* Of the total number of 87 patients, 45 (52 per cent) showed sclerosis of the large intrapulmonary veins (average degree 0.8+). Of the 25 patients less than 40 years of age, 8 (32 per cent) showed sclerosis (average degree, 0.7+). Of the 62 patients over 40 years of age, 37 (60 per cent) showed sclerosis (average degree, 0.9+).

mononuclears and sometimes polymorphonuclears. In 1 case in the "cardiac disease" group the media was notably thick and muscular.

Apart from the presence of inflammatory changes in the walls of veins near abscesses or foci of tuberculosis, the chief differences in the various etiologic groups were that in some cases of heart disease (usually with congestive failure) the thickened intima contained elastic tissue, which was unusual in other groups, and that in 1 case of congestive failure the media was thick and muscular.

Large Intrapulmonary Veins.—Sclerosis of the veins more than 1 mm. in external diameter, contrary to the statements of Ljungdahl [176] and Moschowitz,[213] was found to be much less common and less severe than that of the small veins (tables 15 and 16). Sclerosis was present in 45 of 87 cases (52 per cent) and was equally common in males and females. Sclerosis was present in 8 of 25 patients under 40 (32 per cent) and in 37 of 62 over 40 (60 per cent).

As these veins are usually collapsed after death, it is impossible to measure their external diameter accurately, and the thickness of the intima was expressed as a percentage of the thickness of the wall excluding the adventitia. The presence of any connective tissue between the endothelium and the elastica interna was taken as evidence of sclerosis. If the average thickness of the intima was less than 10 per cent of the thickness of the wall of the vein, the sclerosis was graded +; from 10 to 30 per cent, + +; if from 30 to 50 per cent, + + +, and if over 50 per cent, + + + +.

Table 16 shows that there is a tendency for sclerosis of the large veins to increase with the age of the patient even in the absence of factors thought to raise the pulmonary arterial pressure. The sclerosis was increased in frequency, though not appreciably in severity, in the presence of chronic pulmonary disease and in the presence of cardiac disease, alone or with pulmonary disease, and especially if congestive heart failure was present the sclerosis is increased both in frequency and in severity. In the "no cause" group there was slight patchy thickening of the intima in 2 of the 15 patients under 40 and slight uniform thickening in 1. Of the 15 patients over 40, 4 showed slight patchy intimal thickening, and 2, in whom the adventitia showed deposits of tumor, showed fairly marked thickening. In the "cardiac disease" group both patients under 40, who died of congestive heart failure, showed marked thickening of the intima of all the large veins. There was only slight patchy thickening in 2 of the 3 patients over 40, none of whom had congestive heart failure. In the "pulmonary and cardiac disease" group both patients under 40 had congestive heart failure and both showed slight or marked intimal thickening of the large veins.

The histologic picture was similar to that found in the arteries. There was patchy or uniform thickening of the intima of few or many veins in the affected patients. The intimal connective tissue was usually dense and almost acellular, but in 2 cases, near foci of active tuberculosis, it was loose and fibrillar and contained numbers of lymphocytes. Fat was rarely present, being observed both in foam cells and loose in the intimal connective tissue only in the 2 patients under 40 with cardiac disease. Smooth muscle cells were also rare, being noted only in 2 cases. In 1 patient (a boy of 11 with rheumatic heart disease, fibrosis of the lungs and heart failure) many of the veins showed marked uneven intimal thickening by dense, pink-staining connective tissue, in which were many groups of longitudinally directed muscle cells. Numbers of endothelium-lined lumens were present in the thickened intima in 2 cases near foci of active tuberculosis. Elastic tissue was unusual, being observed in only 4 patients, 3 of whom died of congestive heart failure. Occasionally the elastica interna was frayed, fragmented or missing.

TABLE 16.—*Distribution of Sclerosis in Large Intrapulmonary Veins According to Age, Sex and Etiologic Factor* *

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis		Thickness of Intima	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Intima	Average Degree of Sclerosis
			Number	Percentage				Number	Percentage		
No cause	0–39	8	1	13	1 (0–7)	0.1+	7	2	29	2 (0–8)	0.3+
	40–89	10	5	50	5 (0–19)	0.8+	5	1	20	1 (0–4)	0.2+
Pulmonary disease	0–39	4	1	25	2 (0–6)	0.3+	..	..	..	..	.....
	40–89	7	4	57	10 (0–35)	1.0+	11	10	91	9 (0–30)	1.3+
Cardiac disease	0–39	1	1	..	39	3.0+	1	1	..	32	4.0+
	40–89	2	1	..	5 (0–10)	0.5+	1	1	..	3	1.0+
Hypertension	0–39	..	..	..	..	.....	1	0	..	0	0
	40–89	2	1	..	3 (0–6)	0.5+	4	1	..	1 (0–5)	0.3+
Pulmonary and cardiac disease	0–39	2	2	..	25 (10–39)	2.0+	..	..	..	..	.....
	40–89	8	6	75	16 (0–30)	2.3+	2	2	..	20 (18–22)	2.0+
Cardiac disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	1	1	..	13	2.0+	1	0	..	0	0
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	2	1	..	5 (0–11)	1.0+	1	0	..	0	0
Pulmonary disease and hypertension	0–39	..	..	..	..	.....	..	..	..	..	.....
	40–89	2	1	..	5 (0–10)	0.5+	3	2	..	10 (0–19)	1.0+

* The thickness of the intima is expressed as a percentage of the thickness of the wall of the vessel exclusive of the adventitia. Where measurements are given, the first figure is the average and the figures in parentheses represent the extremes.

The media was notably thick and muscular in 20 patients, 9 of whom died of congestive heart failure. In 1 case it was invaded by lymphocytes and capillaries near foci of active tuberculosis. In 1 case the media was invaded by carcinoma cells, and in another, in which there were deposits of carcinoma in the adventitia, the media was infiltrated by lymphocytes and large mononuclears.

Apart from inflammatory changes in veins near tuberculous foci, the chief differences in the etiologic groups are that the intimal thickening was greatest in the cases in the "cardiac disease" and "pulmonary and cardiac disease" groups in which there was congestive heart failure. In these cases the thickened intima often contained fat, smooth muscle cells

TABLE 17.—*Size of the Main Extrapulmonary Pulmonary Veins in the Various Etiologic Groups*

Etiologic Factor	Circumference of the Stem of the Pulmonary Artery, Cm.	Circumference of the Pooled Pulmonary Veins,* Cm.	Circumference of the Pulmonary Veins Expressed as a Percentage of the Diameter of the Stem	Cross-Sectional Area of the Pulmonary Veins, Percentage†
No cause	7.5 (5.8–9.1)	5.7 (4.1–7.8)	76 (62–89)	63 (50–81)
Pulmonary disease	7.8 (6.4–9.0)	6.2 (4.9–8.0)	77 (58–91)	63 (52–71)
Cardiac disease	8.0 (7.3–9.0)	6.0 (5.3–6.7)	73 (65–84)	55 (49–60)
Hypertension	8.5 (6.5–10.3)	6.0 (4.5–8.0)	69 (61–85)	50 (37–61)
Pulmonary and cardiac disease	8.0 (6.8–9.7)	6.9 (5.2–9.7)	88 (79–141)	90 (61–196)
Cardiac disease and hypertension	9.6 (9.2–10.3)	7.3 (6.1–9.1)	76 (67–88)	56 (45–78)
Pulmonary and cardiac disease and hypertension	8.3 (7.7–8.8)	7.6 (4.9–10.5)	91 (64–124)	91 (35–142)
Pulmonary disease and hypertension	8.3 (6.5–10.2)	6.5 (5.0–7.7)	80 (75–87)	61 (57–66)
Congestive heart failure	8.8 (6.8–10.3)	7.6 (5.6–10.5)	87 (69–141)	90 (50–196)

* By the circumference of the pooled pulmonary veins is meant the circumference of a single vessel of the same cross-sectional area as the four pulmonary veins together.
† The cross-sectional area of the pulmonary veins is expressed as a percentage of the cross-sectional area of the stem of the pulmonary artery.

and elastic tissue, which were not present in the other groups and thickening and muscularity of the media were commoner in these cases than in the others.

Main Extrapulmonary Pulmonary Veins.—These were examined in only the last 38 cases of the series. Sclerosis was never seen with the naked eye. Table 17 shows the size of the main pulmonary veins in the various etiologic groups. Normally, if the four pulmonary veins had been joined to form a single vessel of the same cross-sectional area as the four combined, this vessel would have had a circumference of from 4.1 to 7.3 cm. (average, 6.3 cm.); this is equivalent to from 69 to 93 per cent (average, 78 per cent) of the circumference of the corresponding stem of the pulmonary artery, and to from 48 to 86 per cent (average, 61 per cent) of the cross-sectional area of the stem of the pulmonary artery in each case. The table shows that the veins were dilated in the

"pulmonary and cardiac" disease and "pulmonary and cardiac disease and hypertension" groups, which contained cases of congestive heart failure. This is also shown if all the cases of congestive failure are collected together. In 2 of these cases the capacity of the veins was much greater than that of the stem of the pulmonary artery.

Table 18 shows that although sclerosis was never seen macroscopically it was observed microscopically in 25 cases (66 per cent). The presence of any connective tissue between the endothelium and the elastica interna was taken as evidence of sclerosis. If the intima was less than 0.1 mm. thick and less than 20 per cent of the thickness of the wall of the vein, exclusive of the adventitia, the sclerosis was graded +; if it was from 0.1 to 0.2 mm. thick, or from 20 to 50 per cent of the

TABLE 18.—*Distribution of Sclerosis of the Main Extrapulmonary Pulmonary Veins According to Age and Sex*

	Males			Females		
Age, Years	Number of Patients	Patients with Sclerosis	Average Degree of Sclerosis	Number of Patients	Patients with Sclerosis	Average Degree of Sclerosis
0- 9	..	..	.....	3	0	0
10-19	2	1	1.5+	..	..	.....
20-29	1	0	0	1	1	3.0+
30-39	2	1	1.0+	2	0	0
40-49	5	4	1.0+	2	1	1.0+
50-59	5	4	1.6+	3	2	0.7+
60-69	5	4	1.6+	2	1	0.5+
70-79	2	2	2.0+	3	3	2.0+
80-89	..	..	.....	1	1	1.0+
Totals*.....	22	16 (73 per cent)	1.4+	16	9 (57 per cent)	0.9+

* Of the total number of 38 patients, 25 (66 per cent) showed sclerosis of the main extrapulmonary pulmonary veins (average degree, 1.2+). Of the 11 patients less than 40 years of age, 3 (27 per cent) showed sclerosis (average degree, 0.7+). Of the 27 under 40 years of age, 22 (82 per cent) showed sclerosis (average degree, 1.4+).

thickness of the wall, + +, and if it was over 0.2 mm., or over 50 per cent of the thickness of the wall, + + +. Of 11 patients under 40 sclerosis was present in 3 (27 per cent), while of 27 patients over 40 sclerosis was present in 22 (82 per cent).

Table 19 shows that sclerosis is uncommon and slight in patients under 40 but that it is rather commoner, though still slight, in those over 40, in the absence of factors that are thought to raise the pulmonary arterial pressure. The presence of pulmonary or cardiac disease or both increased the frequency and severity of the sclerosis of the main pulmonary veins in patients both over and under 40, particularly in patients with congestive heart failure. The increased frequency and severity in patients with chronic pulmonary disease are noteworthy, since there the pressure in the pulmonary veins might be expected, if anything, to be reduced, as the abnormal resistance to the pulmonary circulation is provided by the capillaries.

TABLE 19.—*Distribution of Sclerosis of the Main Extrapulmonary Pulmonary Veins According to Age, Sex and Etiologic Factor* *

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis	Thickness of Intima,† Percentage	Thickness of Media, Mm.	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis	Thickness of Intima,† Percentage	Thickness of Media, Mm.	Average Degree of Sclerosis
No cause	0–39	1	0	0	0.224	0	3	1	5 (0–16)	0.277 (0.232–0.349)	0.3+
	40–89	4	2	12 (0–33)	0.307 (0.166–0.448)	0.7+	1	1	20	0.299	1.0+
Pulmonary disease	0–39	2	0	0	0.108 (0.083–0.133)	0	1	0	0	.....	0
	40–89	7	6 (86%)	18 (0–65)	0.228 (0.059–0.493)	1.3+	5	3 (60%)	12 (0–23)	0.220 (0.116–0.332)	0.8+
Cardiac disease	0–39	..	..	..	.....	.....	1	1	40	0.266	2.0+
	40–89	1	1	20	0.232	2.0+	..	..	..	.....	.....
Hypertension	0–39	..	..	..	.....	.....	..	..	..	.....	.....
	40–89	..	..	..	.....	.....	2	1	24 (0–48)	0.249 (0.083–0.415)	1.0+
Pulmonary and cardiac disease	0–39	2	2	40 (36–44)	0.423 (0.285–0.581)	2.0+	..	..	..	.....	.....
	40–89	2	2	27 (13–61)	0.216 (0.183–0.270)	1.5+	1	1	13	0.137	1.0+
Cardiac disease and hypertension	0–39	..	..	..	.....	.....	..	..	..	.....	.....
	40–89	1	1	28	0.249	2.0+	..	..	..	.....	.....
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	.....	.....	..	..	..	.....	.....
	40–89	1	1	27	0.499	2.0+	1	1	2	0.323	1.0+
Pulmonary disease and hypertension	0–39	..	..	..	.....	.....	..	..	..	.....	.....
	40–89	1	1	50	0.232	3.0+	1	1	60	0.249	3.0+

* When measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.
† The thickness of the intima is expressed as a percentage of the thickness of the wall of the vein exclusive of the adventitia.

The histologic changes (fig. 8) were similar to those in the arteries. There was patchy or uniform thickening of the intima by connective tissue, which was usually dense and almost acellular and stained pink with Van Gieson's stain. In 2 cases there were foci of lymphocytes in the thickened intima. In 1 case the thickened intima contained fat both in foam cells and lying free. A little fine elastic tissue was present in 8 cases, and in 1 case there was a great deal of irregular elastic tissue. In 1 case (that of a woman with active rheumatic heart disease) there were foci of lymphocytes not only in the intima but also in the media and adventitia.

Muscularity of the Veins.—No measurements were possible of the amount of muscle in the media of the main intrapulmonary and extra-

Fig. 8.—Photomicrograph of a section of a main extrapulmonary vein (× 20; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). From above downward there are the moderately thickened intima, the media, a narrow zone of fibrofatty tissue, a thick layer of muscle, including heart muscle (at the junction of the left auricular sleeve) and the adventitia consisting of fibrous tissue with some elastic fibers.

pulmonary veins, as it was usually irregularly scattered. The muscularity was graded as "little" when there were only a few muscle fibers in the medial connective and elastic tissue, this probably representing the normal; "moderate" when muscle formed from one fourth to one half of the media (this is perhaps excessive, though it may represent the upper limit of the normal), and "excessive" when most of the media consisted of muscle and thick strands of smooth muscle, distinct from the sleeve of cardiac muscle, were also present in the adventitia. Excessive muscularity was present in 22 of 84 cases (26 per cent) and showed

no appreciable difference with age or sex (table 20). Table 21 shows that excessive muscularity was commonly present in patients with heart disease, either with or without pulmonary disease and hypertension,

TABLE 20.—*Distribution of the Muscularity of the Large Intrapulmonary and Extrapulmonary Pulmonary Veins According to Age and Sex*

Age, Years	Males				Females			
	No. of Patients	Degree of Muscularity*			No. of Patients	Degree of Muscularity*		
		Little	Moderate	Excessive		Little	Moderate	Excessive
0–9	1	1	..	..	3	3	..	..
10–19	9	7	..	2	..	..	..	..
20–29	1	..	1	..	1	..	..	1
30–39	4	1	2	1	4	2	1	1
40–49	7	4	2	1	3	2	..	1
50–59	13	4	4	5	7	5	2	..
60–69	12	6	3	3	8	5	1	2
70–79	4	..	2	2	5	3	..	2
80–89	..	..	..	..	2	1	..	1
Totals†	51	23	14	14 (27 per cent)	33	21	4	8 (24 per cent)

* The terms little, moderate and excessive refer to the estimated amount of muscle in the walls of the veins and are defined in the text.

† Of the 84 patients, 44 showed little, 18 moderate and 22 (26 per cent) excessive muscularity. Of the 23 patients less than 40 years of age, 14 showed little, 4 moderate and 5 (22 per cent) excessive muscularity. Of the 61 patients over 40 years of age, 30 showed little, 14 moderate and 17 (28 per cent) excessive muscularity.

TABLE 21.—*Distribution of Muscularity of the Large Intrapulmonary and Extrapulmonary Pulmonary Veins According to Age and Etiologic Factor*

Etiologic Factor	Age, Years	No. of Patients	Degree of Muscularity*		
			Little	Moderate	Excessive
No cause	0–39	13	11	1	1
	40–89	14	10	4	..
Pulmonary disease	0–39	4	2	1	1
	40–89	18	12	3	3
Cardiac disease	0–39	2	..	..	2
	40–89	3	..	1	2
Hypertension	0–39	1	1	..	..
	40–89	6	4	1	1
Pulmonary and cardiac disease	0–39	3	..	2	1
	40–89	10	1	4	5
Cardiac disease and hypertension	0–39	..	..	..	..
	40–89	2	..	..	2
Pulmonary and cardiac disease and hypertension	0–39	..	..	..	..
	40–89	3	1	..	2
Pulmonary disease and hypertension	0–39	..	..	..	..
	40–89	5	2	1	2

* The terms little, moderate and excessive refer to the estimated amount of muscle in the walls of the veins and are defined in the text.

particularly if heart failure was present. It is possible that the increased muscularity might be an adaptation to an increased pressure in the pulmonary veins, though a similar excessive muscularity was sometimes present in patients without heart disease or heart failure and even in patients with chronic pulmonary disease in whom the pressure in the

pulmonary veins might be expected to be below normal. However, the great frequency of excessive muscularity in patients with heart disease with or without pulmonary disease and hypertension (15 of 21 patients, or 71 per cent, compared with 7 of the remaining 63 patients, or 11 per cent) seems too marked to be accidental.

Systemic Vessels.—These were examined macroscopically and microscopically in every case, particularly the aorta and the coronary, renal and splenic vessels. Various grades of sclerosis were found in 92 of the 100 patients, the exceptions all being in patients under 40. Syphilitic aortitis was found in 9 cases. There was no correlation between the changes in the systemic and pulmonary vessels except that in both it was evident that sclerosis increased in frequency and severity with age.

(To be continued)

URTICARIA DUE TO SENSITIVITY TO COLD

SURVEY OF THE LITERATURE AND REPORT OF A CASE, WITH EXPERIMENTAL OBSERVATIONS

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Attention has recently been drawn to the occasional occurrence of sensitivity to such physical agents as heat, cold or pressure. Patients with such sensitivity react to the local stimulus with an urticarial wheal and may in addition show a general constitutional reaction. Duke[1] in this country has devoted particular attention to this subject. Cases falling in this category have been reported with increasing frequency, especially in the German literature. Investigation of the mechanism of these reactions has yielded many interesting facts, many of them at marked variance with one another, but the etiology has not yet been determined. Many writers have considered the reaction to be allergic or immunopathologic, others, the result of alteration of the colloidal state of the blood and others, the result of altered mechanism of the central nervous system or of peripheral neurovascular mechanisms. Urbach and Fasal,[2] impressed with the conflicting mass of data on the subject, have considered that the etiology is not unitary but may be the result of changes in one sort of mechanism in one case and of another mechanism in another. They have stressed the need of a careful study of the individual case and have advised that therapy be based on the results obtained.

Cases of sensitiveness to cold as described in the literature have been divided into several classes. In the first group fall cases in which a purely local sensitivity is exhibited without an accompanying general, constitutional or systemic reaction. The second group comprises cases

From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Duke, W. W.: (*a*) Heat and Effort Sensitiveness: Cold Sensitiveness; Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Noninfectious Coryza and Infections, Arch. Int. Med. **45**:206 (Feb.) 1930; (*b*) Clinical Manifestations of Heat and Effort Sensitiveness: Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Noninfectious Coryza and Infections, J. Allergy **3**:257, 1932; (*c*) Treatment of Heat and Effort Sensitiveness and Cold Sensitiveness and Treatment of Contact Urticaria Caused by Light, Cold and Scratches, ibid. **3**:408, 1932; (*d*) Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Functional Cardiac Disorders Including Angina Pectoris, Tachycardia and Ventricular Extrasystoles, ibid. **4**:38, 1932.

2. Urbach, E., and Fasal, F.: Vasoallergie oder Vasoneuropathie als Ursache von Kälte-, Wärme- und Druckurtikaria? Ein Beitrag zur Pathogenese und Therapie der sogenannten physikalischen Allergien der Haut, Wien. klin. Wchnschr. **46**:1069, 1933.

in which there is a local reaction with an accompanying systemic reaction. In this group the constitutional symptoms may appear following the exposure of small and restricted areas, but more often the local whealed area must be extensive before a general reaction is elicited. Persons showing no general reaction on exposure of a small area to cold may show such a response when a larger area is exposed. Duke inferred the existence of a third group in which a systemic or remote reaction occurred on local stimulation but without a local reaction.

In cases of the first group, that is, those in which there is a purely local reaction, the patient notices after a varying period following exposure to cold that the erythema which occurs in normal persons gives way to a wheal, sharply limited to the exposed area and accompanied by itching and burning. Harris, Lewis and Vaughan [3] and Horton and Brown [4] found that the reaction does not occur as long as the part is kept in contact with cold but appears a short time after removal from that contact. Freund [5] has noted the occurrence of local reactions after almost unbelievably long latent periods following exposure to cold. The wheal may be transient or may last several hours or longer. In most of the cases reported the patient showed sensitivity of this type over the entire cutaneous area, but a few showed sensitivity on only certain areas of the skin,[6] and some reacted more strongly on one part than another. Some patients show a sensitivity of the buccal or pharyngeal mucosa. As a rule the patient is aware of his own sensitivity, but in rare instances it is only accidentally discovered.[7] The swelling of the hands may be so marked as to interfere with movement of the fingers. The patient's face may be so sensitive that after exposure to a cold wind the eyes may be partially closed or the features indistinguishable.[1b] The symptoms commonly have their onset after swimming,[8] after bath-

3. Harris, K. E.; Lewis, T., and Vaughan, J. M.: Hemoglobinuria and Urticaria from Cold Occurring Singly or in Combination; Observations Referring Especially to the Mechanism of Urticaria with Some Remarks upon Raynaud's Disease, Heart **14**:305, 1927.

4. Horton, B. T., and Brown, G. E.: Systemic Histamine-Like Reactions in Allergy Due to Cold, Am. J. M. Sc. **178**:191, 1929; J. Allergy **1**:193, 1929.

5. Freund, E.: Ueber Latenitz und Spätreaktion nach Kälteschädigung, Ztschr. f. d. ges. phys. Therap. **32**:163, 1926.

6. (*a*) Musger, A.: Quoted by Urbach and Fasal.[2] (*b*) Bernstein, T.: Zum allergischen Charakter der Kälteurtikaria, Dermat. Ztschr. **64**:242, 1932.

7. Fraser, T. R.: Urticaria e Frigore, Tr. Med.-Chir. Soc. Edinburgh **25**:90, 1905.

8. (*a*) Netter: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:339, 1921. (*b*) Lehner, E.: Kälteurtikaria, Klin. Wchnschr. **8**:306, 1929. (*c*) Graszl: Zur Frage des Badetodes, München. med. Wchnschr. **79**:1469, 1932. (*d*) Thannhauser, S. J.: Zur Frage des Badetodes, ibid. **79**:1890, 1932. (*e*) zum Busch, J. P.: Ueber plötzlichen Tod im kalten Bade, Deutsche med. Wchnschr. **59**:15, 1933. (*f*) Affolter, J.: Urticaria et syncope "a frigore," Schweiz. med. Wchnschr. **63**: 881, 1933.

ing [9] or washing in cold water,[10] after being out in a cold wind or snow and after eating ice cream [11] or drinking cold liquids. Often, as noted by Duke, the condition is first noted after an acute illness. Duke was also impressed with the fact that the reaction is inhibited during febrile illnesses, during an artificially induced fever and following exercise and in the early morning hours. He expressed the opinion that patients with a reaction of this type are hypersusceptible to infection. They are as a rule very active. Duke and Bray [12] noted that such persons have a constantly subnormal and irregular temperature. In a long-standing case a recurrent form of eczema may be established, with seasonal exacerbations.[13]

In the second group of cases, either simultaneous with [1b] or after a latent period of a few minutes following [4] the appearance of the wheal there occurs a systemic reaction characterized by a fall in blood pressure,[14] a sharp rise in the pulse rate,[8f] flushing of the face and ears and a tendency to syncope [8f] with recovery after a variable period of time. There may be headache, rigor, dyspnea, cough, generalized aches and pains or transient blindness.[15] There may or may not be associated hemoglobinuria,[16] and this seems more likely to occur in persons with syphilis.[17] Several German authors [18] have suggested that many of the accidents by drowning which occur each year even to excellent swimmers may be explained by sensitivity to cold. Tests carried out

9. Negel: Oedèmes éphémères de nature arthritique, Progrès méd. **12**:846, 1884. Netter.[8a]

10. Schlenker, H.: Zur Behandlung der Kälte-Anaphylaxie, München. med. Wchnschr. **80**:974, 1933.

11. (*a*) Blachez: Procès-verbal de la séance du 8 Nov. 1872, Bull. et mém. Soc. méd. d hôp. de Paris **9**:270, 1872. (*b*) Wallace, T. I.: A Case of Bronchial Asthma Accompanied with Urticaria Brought on by Eating Ice Cream, Australasian M. Gaz. **28**:436, 1909. Lehner.[8b]

12. Bray, G. W.: A Case of Physical Allergy: A Localized and Generalized Allergic Type of Reaction to Cold, J. Allergy **3**:367, 1932.

13. Bernstein, F.: Beiträge zu den physikalischen Idiosynkrasien der Haut: III. Kälteekzem, Arch. f. Dermat. u. Syph. **168**:103, 1933. Duke.[16]

14. (*a*) Ito, M., and Kobayashi, E.: Un cas d'urticaire par le froid chez un hérédosyphilitique, Jap. J. Dermat. & Urol. **30**:87, 1930. (*b*) Riehl, G., Jr., and Risek, E.: Zur Pathogenese der Kälteurticaria und ihrer Zusammenhänge mit der paroxysmalen Hämoglobinurie, Ztschr. f. klin. Med. **124**:29, 1933. (*c*) Horton and Brown.[4] Bray.[12] Affolter.[8f] Wilder [15a] described a rise in blood pressure in his case.

15. (*a*) Wilder, J.: Kälteurtikaria mit schweren Allgemeinerscheinungen, Wien. klin. Wchnschr. **45**:1458, 1932. (*b*) Urbach, E., in discussion on Wilder.

16. Harris, Lewis and Vaughan.[3] Riehl and Risek.[14b]

17. (*a*) Moss, W. L.: Paroxysmal Hemoglobinuria: Blood Studies in Three Cases, Bull. Johns Hopkins Hosp. **22**:238, 1911. Numerous additional references are contained in the article by Harris, Lewis and Vaughan.[3] (*b*) Forrest, R. W.: Case of Paroxysmal Haematinuria, Glasgow M. J. **11**:421, 1879.

18. Lehner.[8b] Graszl.[8c] Urbach.[15b] Thannhauser.[8b] Bernstein.[6b] Zum Busch.[8e] Affolter.[8f]

on subjects surviving these accidents showed them to react to cold in the same way as patients in the second group.

In the third group fall numerous cases of bronchial asthma,[11b] vasomotor rhinitis and conjunctivitis, photophobia, abdominal pain, erythema, pruritus, urticaria, angioneurotic edema, eczema and shock, conditions believed by Duke [1a] to be caused in some patients specifically and solely by the physical action of cold. He commented on the well known association of exposure to cold and anginal attacks and described a case in which ventricular extrasystoles could be brought on by cold and inhibited by heat.

At least three major lines of investigation have been followed in the elucidation of the etiology of these reactions. The first has been immunologic, concerning antigen-antibody reactions; the second, humoral, concerning the liberation of certain chemical substances, and the third, neurovascular, concerning altered nervous or vascular mechanisms.

THE IMMUNOLOGIC HYPOTHESIS

The method of passive transfer as worked out by Prausnitz and Küstner has been used to test immunologic specificity. Blood is removed from a vein of the arm of a patient at the height of the local and systemic reaction caused by cold, and the serum is separated and injected intracutaneously into a normal nonallergic person. The slight swelling from the injection is allowed to subside. Then cold is applied, and a wheal appears. Serum treated similarly from a normal person causes no wheal. Positive results were obtained by Harris, Lewis and Vaughan,[3] Covisa and Prieto,[19] Lehner,[20] Lehner and Rajka,[21] Liebner [22] and Bernstein [6b] among others. Jadassohn and Schaaf,[23] Perutz, Brügel and Grünfeld,[24] Klein,[25] Marquardt,[26] Benjamin [27] and others were unable to obtain the Prausnitz-Küstner reaction in their cases.

19. Covisa, J. S., and Prieto, J. Gay: Contribucion al estudio de la urticaria al frio, Dermat. Wchnschr. **91**:1188, 1930.

20. Lehner, E.: Zentralbl. f. Dermat. **41**:199, 1932; quoted by Urbach and Fasal.[2] Lehner.[8b]

21. Lehner and Rajka: Arch. f. Dermat. **158**:402, 1929; quoted by Urbach and Fasal.[2]

22. Liebner: Zentralbl. f. Dermat. **34**:406, 1930; quoted by Urbach and Fasal.[2]

23. Jadassohn, W., and Schaaf, F.: Kälteurticaria bei zwei Geschwistern, Dermat. Wchnschr. **86**:565, 1928.

24. Perutz, A.; Brügel, S., and Grünfeld, R.: Zur Pathogenese der Kälteurticaria, Klin. Wchnschr. **8**:1999, 1929.

25. Klein, A. E.: Zur Frage der durch Wärme and Kälte ausgelösten Urtikaria, Dermat. Wchnschr. **95**:1741, 1932.

26. Marquardt, F.: Untersuchungen bei Kälteurticaria und Urticaria factitia, Dermat. Wchnschr. **96**:261, 1933.

27. Benjamin, C. E.: Zes Gevallen von Koude-Allergie, Nederl. tijdschr. v. geneesk **77**:4461, 1933

Harris, Lewis and Vaughan [3] demonstrated in the serum of a patient showing both urticaria due to cold and paroxysmal hemoglobinuria the presence of a hemolytic amboceptor and a dermolytic amboceptor. They believed the response of the skin to cooling in the Prausnitz-Küstner test to be due to the presence of a dermolysin in the patient's blood; this unites with the skin at a low temperature only, and the reaction occurs after the skin is rewarmed. Their conception is that just as the hemolysin combines with the red blood cell membrane at a low temperature with subsequent alteration of its permeability so that the hemoglobin content of the cell is liberated into the serum, so does the dermolysin combine with the cutaneous cell at a low temperature, causing change in its permeability and thus bringing about the release of the contents of the cell into the intercellular medium.

The phenomenon of specific exhaustion is also invoked as attesting the immunologic nature of these reactions. After the reaction once produced has subsided, reapplication of the same stimulus—cold—for the same period becomes less and less capable of producing a wheal, while the immediately adjacent and previously untouched skin is reactive. This observation forms the basis for therapy by specific desensitization advocated by many writers.[28] By daily immersion of the parts in cold water of decreasing temperature for increasing periods, excellent results have been reported.

The specificity of the reaction has also been regarded as favoring its immunologic nature. In cases of sensitivity to physical agents symptoms as a rule are caused specifically by one physical agent only,[3] although occasionally by two or more.[29] Patients sensitive to material substances rarely react specifically to the action of physical agents, and vice versa. Harris [30] found that of several patients with urticaria due to specific factors, such as light, cold or cat, none had a dermatographic wheal when skin was stroked; that is, none were sensititve to mechanical stimulation.

Another line of reasoning is the similarity of these phenomena to allergic or anaphylactic reactions which have been considered immune reactions. Numerous investigators, particularly the French and Italian,[31]

28. (*a*) Schutz, J.: Mittheilungen über eine häufiger vorkommende Form von Urtikaria chronica recidiva, München. med. Wchnschr. **42**:798, 1895. Duke,[1c] (*b*) Vallery-Radot, P., and Blamoutier, P.: Urticaire par le froid: Traitement par l'accoutumance, Bull. et mém. soc. méd. d. hôp. de Paris **47**:1907, 1931.

29. Henry, J. P.: J. Allergy **1**:194, 1929. Duke.[1a]

30. Harris, K. E.: Urticaria: Observations upon the Vascular Reactions in the Skin, Quart. J. Med. **24**:347, 1931.

31. Gougerot; Peyre, Moutet and Bourdillon: Urticaire par le froid, Bull. Soc. franç. de dermat. et syph. **34**:321, 1927. Joltrain, E.; Morat, D., and Ley, J.: Urticaire géante: Observée chez un morphinomane à chaque tentative de sèvrage, Presse méd. **35**:1361, 1927. Covisa and Prieto.[19] Marquardt. [26] Urbach and Fasal.[2]

have been able to follow the lead of Widal and his associates [32] and have shown that these reactions, like anaphylactic responses in general, are characterized by an abrupt fall in the leukocyte count. Other workers could not demonstrate this so-called hemoclastic crisis,[33] and Lehner [5b] found that instead of falling the white blood cell count rose. Eosinophilia has occasionally been observed in these cases.[34] Bray [12] stated that eosinophilia is rare, but he was able to demonstrate local eosinophilia in a wheal due to sensitivity to cold. An instance of familial occurrence of the condition was described by Jadassohn and Schaaf.[23] Bray's patient had a strong family history of asthma, while the patient described by Widal, Abrami and Lermoyez [32] later had nasal polyps and asthma.

THE HUMORAL HYPOTHESIS

Harris, Lewis and Vaughan found the reaction to cold to be of the usual type seen in cases of cutaneous injury, namely, an acute triple response with local dilatation of arterioles, venules and capillaries followed by the formation of wheals and the surrounding flare due to arteriolar dilatation caused by a local axon reflex. They explained the systemic reaction following the local response as the result of the diffusion of a histamine-like substance into the blood stream by which it is carried to remote parts of the body. These workers, as well as Horton and Brown,[4] Lehner and Rajka [21] and Bray,[12] were able to show that with a tourniquet applied so as to cut off the venous return from the hand or the arterial supply to the hand before it was immersed in the cold water and kept on for an additional period after the hand was removed from the cold environment a local response was produced but a systemic reaction did not occur. When the tourniquet was released the systemic reaction took place. Horton and Brown [35] adduced further evidence in favor of the release of a histamine-like body in a patient in whom a rise in the free acidity of the gastric juice from 0 to 54 units followed the local reaction. The effective treatment by Bray [12] of his patient with sensitivity to cold, in whom he was able to bring about desensitization to cold by the injection of histamine, may also be pertinent. Marquardt's experience with the tourniquet test was at marked variance with the foregoing observations.[26] In three cases he found that a local wheal did not form if a tourniquet had previously been applied and that the wheal appeared only when the circulation was

32. Widal, F.; Abrami, P., and Lermoyez, J.: Anaphylaxie et idiosyncrasie, Presse méd. **30**:189, 1922.

33. Vallery-Radot and Blamoutier.[28b] Perutz, Brügel and Schaaf.[24] Riehl and Risek.[14b] Klein.[25]

34. Affolter.[8f] Marquardt.[26]

35. Horton, B. T., and Brown, G. E.: Histamine-Like Effects on Gastric Acidity Due to Cold, Proc. Staff Meet., Mayo Clin. **7**:367, 1932.

restored. General reactions did not occur in his first case and were not mentioned in the reports on the other two. Duke and Wagner [36] found that the local and general reactions were independent of the application of the tourniquet.

THE NEUROVASCULAR HYPOTHESIS

Duke,[1a] having found that no systemic reactions followed if heat was applied to one peripheral area while cold was applied to another area in persons sensitive to cold, concluded that the general reaction has much to do with the actual sensation of cold. He conceived of the entire condition being due to an imbalance of the mechanism for the regulation of heat. He emphasized the factors of the history of previous infection, the courses of subnormal temperature and the inhibition of the reaction during spontaneous or artificially induced fever. Wilder,[15a] trying to carry the idea of involvement of the central nervous system one step further, found in his case of urticaria caused by cold that the suggestion of cold in hypnosis did not cause the formation of a wheal. Perutz, Brügel and Grünfeld [24] focused their attention on the peripheral rather than the central nervous mechanism and found that rubbing the skin of a patient with menthol, which specifically stimulates the cold receptors of the skin, either causes an abortive wheal or sensitizes the skin so that a wheal is more readily produced on the subsequent application of cold. They concluded that urticaria caused by cold is due to a vasoneurosis of the receptors of cold (peripheral nerve endings). These results have not been confirmed.

Although it is commonly stated that syphilis is a common cause of the occurrence of urticaria due to cold, a glance at the literature shows the concurrence to be infrequent. The syphilitic cases may [37] or may not [38] be associated with paroxysmal hemoglobinuria. Some cases of nonsyphilitic persons have been reported in which both hemoglobinuria and urticaria caused by cold were exhibited.[14b]

REPORT OF CASE

History.—A housewife 36 years old was admitted to the Peter Bent Brigham Hospital on Dec. 15, 1933. She ate some sherbet late one afternoon in June. While eating it she noticed a sense of constriction in the throat. That evening she felt very sick, experienced numerous aches and pains throughout her body and had great difficulty in catching her breath. She felt the disturbance through the night and awoke at about 1 o'clock in the morning with severe pains in the back. It was very hot, and when she awoke she was uncovered. She had a moderately severe cold in the head for the next four or five days. On the fourth

36. Wagner, R.: Wind- und Kälteurtikaria bei Lues hereditaria, Dermat. Wchnschr. **74**:489, 1922.

37. Moss.[17a] Forrest.[17b] Harris, Lewis and Vaughan.[3]

38. Kleeberg: Kälteurticaria, Berl. klin. Wchnschr. **58**:581, 1921. Wagner.[36] Ito and Kobayashi.[14a]

day, feeling somewhat better, she noticed for the first time that any part of her body would swell when it touched a cold object, for example, when her feet touched the cold floor or her hands touched the cold tile of the bathroom fixtures. The swelling thus occasioned would persist for from several hours up to more than a day. This condition of sensitivity to cold persisted up to the time of admission to the hospital and was the patient's complaint on admission. Whenever her hands were exposed to cold there developed, first, a local reddening, followed by a sharply demarcated blanched swelling, bordered by a thin, fading, reddish area. This was associated with a stinging, throbbing sensation "as if all the blood in the body had rushed to the hands." The hands would remain swollen for several hours. She found that plunging the swollen hands into warm water would hasten the disappearance of the swelling. On two occasions while washing vegetables in cold water her hands became swollen to two or three times their normal size and remained so for three days. She also noticed in going outdoors on a cold day that her nose felt "hard" and "puffed." She also found that swelling and tingling of the tongue and throat developed and that she had difficulty in swallowing when she took cold solid or liquid food. About a month after the onset of the difficulty the patient ventured to go in swimming, but her body soon began to tingle, and there developed generalized small white wheals so that she had to leave the water.

It is important to note that the patient had eaten sherbet on several occasions before the apparent inciting episode, but without ill effect. The severity of the symptoms of swelling on exposure to cold seemed to have abated during the month or two preceding admission to the hospital. At first the swelling was associated with weakness, malaise and generalized aches and pains, but the patient never lost consciousness. More recently systemic reaction was less and less prone to follow.

The patient had never been sensitive to the effects of excessive heat nor had she ever had hematuria or a history suggestive of paroxysmal hemoglobinuria. There was no personal or family history of any allergic condition. The menstrual periods were always regular. She had three children, all of whom were well. Her usual weight was about 137 pounds (62.1 Kg.), and during the six months preceding admission to the hospital she gained about 5 pounds (2.3 Kg.).

Cutaneous tests done elsewhere with the common cereals, egg and milk showed the patient to react positively to barley and questionably to rye and milk, and attempts were made to desensitize her to these. Extraction of several abscessed teeth was likewise recommended and carried out. She was also told to avoid fresh fruits and vegetables, which advice she followed. Desensitization by increasing exposure to progressively colder baths was also advised.

Examination.—Physical examination on admission gave negative results except for a faint systolic murmur at the base of the heart and a reddened pharynx.

The red blood cell count was 4,150,000 per cubic millimeter; the hemoglobin content was 78 per cent (Sahli), and the white blood cell count was 10,000. A stained smear showed a differential count of 68 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes, 6 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. The red blood cells and platelets were normal in appearance. Examination of the urine gave negative results. The Wassermann and Hinton reactions of the blood were negative. The stools were normal. The basal metabolic rate was — 6 per cent.

Experimental Observations.—During the patient's stay in the hospital and while she was being followed in the outdoor department numerous observations were made. It was found that urticaria followed the application of ice or water at from 0 to 20 C.

Attempts to carry out the reaction of passive transfer (Prausnitz-Küstner reaction) were unsuccessful. Blood was removed aseptically from the antecubital veins draining the hand both before and twenty-two minutes after exposure to ice-water for five minutes (nineteen minutes after the beginning of visible local swelling). The serums were separated. Neither was capable of causing formation of a wheal when it was injected into the skin of a normal person and ice was subsequently applied. The blood pressure and pulse rate were carefully followed before, during and after the immersion (table 1). Aside from a transient elevation of the blood pressure on first contact with the cold water there was essentially no change, and the patient did not complain of symptoms suggesting shock. There was likewise no significant change in the calcium and potassium content of the

TABLE 1.—*Effect of Local Reaction on the Blood Pressure, Pulse Rate, Cation Relationships and Immunologic Properties of the Blood*

Time	Observations	Blood Pressure	Pulse Rate	Calcium, Mg. per 100 Cc.*	Potassium*	Prausnitz-Küstner Reaction	Hemolytic Amboceptor
2:42	.....	125/74	90	..	..	..	..
2:44	.....	114/75	88	..	..	..	..
2:46	.....	118/73	86	..	..	..	..
2:50	.....	120/72	88	..	..	..	..
2:55	First specimen of blood withdrawn	.....	..	10.2	4.1	Negative	Not present
3:00	.....	120/80	84	..	..	..	..
3:05	Hands immersed in ice-cold water	.....	..	..	..	..	..
3:06	.....	138/92	92	..	..	..	..
3:08	Hand itched; no swelling	130/80	92	..	..	..	..
3:10	Hand was removed from water; hand was red, not swollen; patient complained of throbbing	.....	..	..	..	..	..
3:11	Hand felt numb	120/80	92	..	..	..	..
3:13	Hand began to swell; felt as if "boiling"	.....	..	..	..	..	..
3:15	.....	126/83	88	..	..	..	..
3:19	.....	122/82	86	..	..	..	..
3:28	Swelling was well marked	110/72	86	..	..	..	..
3:32	Second specimen of blood withdrawn	120/80	86	9.7	3.9	Negative	Not present
3:34	.....	122/75	88	..	..	..	..

* These values were determined by Dr. J. C. Aub and Dr. W. T. Salter.

blood serum before and during the reaction. The local swelling did not appear until a few minutes after the hand had been removed from the cold water. This observation was confirmed several times, but the immersion was never maintained for more than ten minutes to determine whether the swelling would occur even if the hand were kept in contact with cold for a longer time. Hemoglobinuria was never produced by the local reaction, and the presence of a hemolysin in the blood before or during the reaction (the technic of Donath and Landsteiner [39] being employed) could not be demonstrated.

In another experiment washings were obtained from a large whealed area by repeatedly injecting and withdrawing sterile physiologic solution of sodium chloride with a 1 cc. hypodermic syringe. This material was capable of causing a persistent wheal in a neighboring cutaneous area while a control injection of physio-

39. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, München. med. Wchnschr. **2**:1590, 1904.

logic solution of sodium chloride failed to do so (fig. 1). Figure 1 shows the "mother" wheal and the small wheal produced by injecting the washings into the neighboring skin.

The finding of local eosinophilia as described by Bray was confirmed in the present case. Capillary blood removed from the ring finger of each hand before the reaction showed an eosinophil count of 1 per cent. After the formation of the wheal capillary blood from the right hand obtained by puncture through the wheal showed a 6 per cent eosinophil count (table 2), while the eosinophil count in blood from the unexposed hand remained at 1 per cent. Blood from a normal person's hand showed no local rise in the eosinophil count following exposure to cold. The patient showed no significant change in the remainder of the leukocyte formula, in the total white blood cell count, in the level of chloride in the venous blood or in the carbon dioxide-combining power.

TABLE 2.—*Effect of Local Reaction on the Red Blood Cell Count, Distribution of Leukocytes, Chloride Content, and Carbon Dioxide-Combining Power*

Location of Test	Red Blood Cells	White Blood Cells	Polymorphonuclears	Lymphocytes	Mononuclears	Eosinophils	Basophils	Chlorides (Whole Venous Blood), Mg. per 100 Cc.	Chlorides (Plasma), Mg. per 100 Cc.	Carbon Dioxide-Combining Power, Vols. %
Before reaction										
Right ring finger	4,160,000	7,200	56	37	5	1	1	...	...	....
Left ring finger	4,150,000	9,000	57	36	6	1	0	...	...	....
Venous blood	.....	.....	..	..	..	..	..	518	566	65.5
Twenty minutes after reaction										
Right (exposed) ring finger	3,530,000	7,400	57	35	2	6	0	...	...	....
Left (unexposed) ring finger	4,080,000	7,400	50	44	5	1	0	...	...	....
Venous blood	.....	.....	..	..	..	..	..	511	563	69.2

An attempt was made to confirm the findings of Perutz, Brügel and Grünfeld, but this was unsuccessful. Local rubbing with a 10 per cent solution of menthol in alcohol so as to produce a distinct local sensation of cold did not cause the appearance of a wheal, nor did it cause the rubbed area to react more readily than the surrounding cutaneous area to the local application of cold. It was also found that stroking the patient's skin either lightly or with heavy pressure did not cause the formation of a wheal. She was not sensitive to the local effect of heat.

Prior anesthesia of the skin with procaine hydrochloride so that ice locally applied was not felt to be cold had no influence on the subsequent development of a wheal on exposure to cold.

During her stay in the hospital the patient had a normal temperature, the buccal temperature ranging around 36.6 C. The cutaneous temperature in a room kept at 22.2 C. and a humidity of 47 per cent was 25.2 C. at the base of the right great toe, which is at the lower range of normal encountered at the Peter Bent Brigham Hospital. The cutaneous temperature was studied before and after the immersion of both arms in a cold water bath at 15.5 C. for five minutes. There was a fall in the

Fig. 1.—A sharply demarcated wheal with borders corresponding to the edges of a piece of ice placed on the skin for five minutes. The wheal has the tough white appearance of pigskin and is surrounded by a fading reddish band. The smaller wheal over the left scapula (*A*) was produced by the intracutaneous injection of washings of physiologic solution of sodium chloride from the larger wheal. Just to the right of this is the hardly perceptible nonwhealed site (*B*) of the control injection of physiologic solution of sodium chloride.

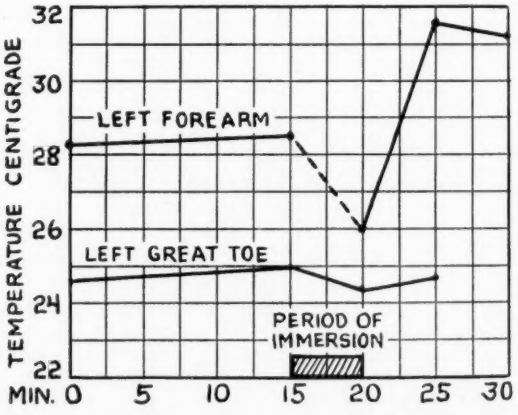

Fig. 2.—A graph indicating the primary fall in the temperature of the skin of the exposed arm with an exaggerated secondary rise in the local temperature. Corresponding but lesser changes took place in the corresponding foot.

cutaneous temperature during the period of immersion, followed by an exaggerated secondary rise. There were concomitant changes in the temperature of the lower extremities with primary fall and secondary less well marked rise. Figure 2 indicates the temperature of the skin of the left forearm and the left great toe before and after the period of immersion. A similar variation of temperature was observed in the right extremities.

Treatment.—Treatment consisted of repeated and increasing exposure to cold in the form of cold showers or rubbing the body with cakes of ice. As stated previously, the patient had already shown a certain degree of improvement when first seen, and it is impossible to state whether the further improvement shown was a natural and spontaneous development or the result of treatment. At the time of writing there is still mild sensitivity but the patient can tolerate from slight to moderate exposure to cold.

COMMENT

From the data obtained in the present case a brief can be held for no particular etiologic theory of urticaria due to cold. The failure to cause the formation of wheals by a local application of menthol which produces a sensation of cold and the failure to inhibit the reaction by a sufficient degree of anesthesia with procaine hydrochloride to make the skin insensitive to cold would seem to make the reaction independent of the nervous mechanism involved in the sensation of cold.

The occurrence of eosinophilia locally may not necessarily predicate an allergic reaction, for it has been shown that eosinophilia of the tissues can be produced just as readily by the intracutaneous injection of histamine as by substances causing an allergic reaction, such as pollens or emanations from animals.[40]

As in the present case, Benjamin [27] reported a rise in the cutaneous temperature of his patient after the removal of the immersed arms from cold water. This was probably due to reactive hyperemia. Hewlett [41] found an increased flow of blood to the arm during the reaction in a similar case in contrast to a diminished flow to the arm of a normal person similarly treated. Affolter [8f] observed an increase in the oscillometric index indicating local vasodilatation.

The fact that no systemic reaction could be induced experimentally does not invalidate the humoral hypothesis, for possibly if a wheal were formed over a more extensive area the concentration of the hypothetic substances diffusing into the blood stream might have been adequate to cause general symptoms. It is conceivable that in the reactions produced a sufficient concentration of these substances diffuses into the intercellular spaces to be capable of transfer to a neighboring area of skin, but that the concentration attained in the blood stream is not

40. Kline, B. S.; Cohen, M. B., and Rudolph, J. A.: Histologic Changes in Allergic and Nonallergic Wheals, J. Allergy **3**:531, 1932.

41. Hewlett, A. W.: Active Hyperemia Following Local Exposure to Cold, Arch. Int. Med. **11**:507 (May) 1913.

enough to produce "shock" reactions or to be demonstrated by the Prausnitz-Küstner technic. It is possible that this criticism may be applied to many of the cases reported in the literature.

SUMMARY

A case of sensitivity to cold manifested in the development of local urticaria is described. The patient, a housewife 36 years old, who was nonsyphilitic, had the condition for one year. The entire cutaneous area and the buccal, pharyngeal and nasal mucosa were sensitive. There was no dermatographia or paroxysmal hemoglobinuria, and no hemolysin could be demonstrated in the blood. Tests for passive transfer were negative, and no systemic reaction followed local reaction experimentally produced. The formation of a wheal was not induced by the local application of menthol or inhibited by anesthesia with procaine hydrochloride. The temperature of the skin, ordinarily at the lower range of normal, showed a secondary rise following the local reaction. Improvement in the condition was either spontaneous or the result of specific desensitization. The etiology has not been determined.

EXPERIMENTAL CONCENTRIC AND ECCENTRIC CARDIAC HYPERTROPHY IN RATS

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Chanutin (with Ferris [1] and with Barksdale [2]) has recently shown that in rats deprived of 80 per cent of their renal tissue progressive renal lesions, arterial hypertension and cardiac hypertrophy develop. The width of the myocardial fibers of the right ventricle does not change, while the diameter of the fibers of the left ventricle bears "a substantial relationship" to the ratio of the weight of the heart to the surface area.

The comparison of a unidimensional or bidimensional method of measurement with a volumetric method has in the past led to serious misinterpretation of data. In this instance there has been no error in conclusions, but the comparison of width of the fibers (a linear measurement) with the weight of the heart (proportional to the total volume of all the fibers) has concealed an important fact, namely, that when the fibers of the heart of the rat hypertrophy in response to arterial hypertension they not only are thicker but are actually shorter than those of the normal rat (table 1).

This, we believe, is the first time that data conclusively proving the existence of concentric hypertrophy have been presented, and the fact seemed sufficiently important to justify further investigation, which has fully corroborated Chanutin's data.

METHODS

Renal insufficiency was produced in one group of rats, and the hypertrophied hearts were compared with the hearts of controls and with the hearts of rats fed desiccated thyroid.

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1. Chanutin, A., and Ferris, E. B.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, Arch. Int. Med. **49**:767 (May) 1932.

2. Chanutin, A., and Barksdale, E. E.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, Arch. Int. Med. **52**:739 (Nov.) 1933.

The rats were male albinos, 95 days of age at the beginning of the experiment. From the time of weaning and throughout the experiment they ate a stock diet containing 10 per cent casein and 18 per cent total protein. Full details of the strain of rats, environment, diet, basic methods and the like have been reported by MacKay and MacKay.[3]

Surface area was computed (without correction for gastro-intestinal content) by the formula $SA = 11.36 \times W^{2/3}$, in which W represents the body weight. The organs were weighed on Hartmann-Braun torsion balances, thus reducing errors of drying to a minimum.

When the animals were killed they were bled, with potassium oxalate as the anticoagulant; the cell volume and concentration of urea were determined on this blood.

TABLE 1.—*Changes in Length of the Fibers and in the Capacity of the Left Ventricle Calculated from the Weight of the Heart and Width of the Fiber* *

Blood Pressure, Mm. Hg	Number of Rats	Heart Weight per 100 Sq. Cm.	Width of Fibers of the Left Ventricle	(A) Left Ventricle, Weight per 100 Sq. Cm.†	(B) Volume of Fibers per μ of Length‡	(C) Length of Fibers (Total) of Left Ventricle§	(D) Relative Capacity of Left Ventricle‖
120 or less	9	188 mg.	15 μ	134 Mg.	177 μ^3/μ	0.76 kilometers	100%
120 to 150	28	188 mg. ±0%	16.6 μ +11%	134 mg. ±0%	217 μ^3/μ +23%	0.62 kilometers −18%	85%
150 to 190	29	238 mg. +26.5 %	20.0 μ +33%	184 mg. +37%	314 μ^3/μ +77%	0.59 kilometers −22%	105%
190 to 230	13	252 mg. +34%	21.6 μ +44%	198 mg. +48%	365 μ^3/μ +106%	0.54 kilometers −29%	103%

* The calculations are based on the data of Chanutin and Barksdale.[2] It is obvious that the increase in the volume of the fibers in the group with blood pressure over 190 is three times as great as the increase in the weight or volume of the heart and two and one-quarter times greater than the increase in the weight of the left ventricle. This involves a shortening of the length of the fibers at least 29 per cent, with no change in the capacity of the ventricle.

† This is calculated on the basis of no change in weight of the right ventricle and on a normal ratio of the weight of the left ventricle to that of the right of 2.47 : 1.

‡ Volume per unit of length equals the radius squared times π.

§ This is determined by dividing the figure in column A by that in column B.

‖ The ventricular capacity is roughly proportional to the 3/2 power of the inner surface area, and the surface area changes with the average width and length of the fibers lining it. The result is calculated by taking the 3/2 power of the product of fiber width times fiber length, each in percentage of the control values.

Renal insufficiency was produced in seventeen rats by a modification of Chanutin's technic, which enabled determination of the amount of renal substance removed. The rat was anesthetized with ether, and the left kidney was delivered through a short incision below the costal margin. After decapsulation of the kidney, a bulldog clamp was applied to the renal pedicle for hemostasis, and the desired amount of tissue was removed at the poles, a ring forceps being used as a guillotine. An assistant weighed the removed tissue immediately. The amount of tissue to be removed was calculated from the surface area of the animal and the known average weight of the kidney of a rat. Thus the renal tissue could be reduced to any desired degree with some accuracy. The renal artery was

3. MacKay, L. L., and MacKay, E. M.: Factors Which Determine Renal Weight: I. Methods, Am. J. Physiol. **83**:179 (Dec.) 1927.

compressed for three minutes, within which time the required amount of tissue was removed. The clamp was then removed, and the kidney was allowed to return to its normal position. The amount of bleeding was small. The application of one catgut suture through the muscle layer and three or four skin clips completed the operation. Five days later the entire right kidney was removed and weighed. There was no attempt at asepsis in either operation.

In addition to the seventeen nephrectomized rats, sixteen male rats of the same age were set aside as controls, and to seven similar rats was fed desiccated thyroid, 0.1 per cent in the stock diet.

Seventy days after the second operation, when all the rats were 170 days of age, they were killed. After being weighed and anesthetized with ether, the rat was exsanguinated. The stump of the kidney (or both kidneys in the case of the controls and rats which had been fed thyroid) was removed and decapsulated. A sagittal incision was made; the surface was blotted on filter paper, and the kidney was weighed.

After the heart was removed, with the auricles and about 0.5 cm. of the great vessels, a blunt needle was introduced into the aorta and the left ventricle irrigated with a 0.9 per cent solution of sodium chloride. After the heart's contents had been expelled by pressure and the heart blotted on filter paper, the heart was weighed.

The heart was then moistened with saline solution and kept overnight at room temperature in a closely stoppered test tube. In from eighteen to twenty-four hours rigor mortis had disappeared. The heart was then removed from the tube; the aorta was cannulated and tied tightly about the glass cannula at the aortic ring and auriculoventricular groove. The left ventricle and cannula were filled with mercury, while the ventricle was manually compressed several times; the massage insured absence of rigor, and the alternate compression and expansion dislodged air and insured complete filling. The column of mercury was then raised to a constant marked height of 80 mm. above the aortic ring, and the entire preparation was weighed. The volume of the left ventricle was calculated by subtracting the weight of the fresh heart and the mercury-filled cannula and dividing by 13.6.

Finally, the ventricle was emptied of mercury, and the heart was fixed in Zenker's fluid and then placed in 80 per cent alcohol. The atria and great vessels were removed and weighed. The heart was divided into two portions along a plane perpendicular to and about the middle of a line from the base to the apex. The outer wall of the right ventricle was removed and weighed. The left ventricle (with the septum) was cleared of as much of the small amount of adherent mercury as possible and weighed. This crude weight of the wall of the right ventricle and of the left ventricle plus the septum was corrected to apportion the septum by means of a comparison of our method of ventricular separation with that of T. Lewis (similar to ours) and that of Herrmann.[4] In view of their data, 30 per cent of the crude weight of the right ventricle was arbitrarily added to the observed value, and an equal amount was subtracted from the observed weight of the left ventricle and septum to give the corrected weights of the right and left ventricles.

The usual statistical methods were used in computing standard deviations and probable errors of the means.

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4. Herrmann, G. R.: Experimental Heart Disease: I. Methods of Dividing Hearts, with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, Am. Heart J. **1**:213 (Dec.) 1925.

RESULTS

At the first operation the mean weight of the removed renal tissue was 102 mg. per hundred square centimeters, or 60 per cent of the mean weight of the single kidneys of the controls. The total removal of the right kidney five days later left the animal with 40 per cent of one kidney, or 20 per cent of the original total renal tissue (neglecting the five day hypertrophy of the stump).

Rats with this much kidney, though progressive polyuria and proteinuria developed and the values for blood urea were from 78 to 514 (mean 231) mg. per hundred cubic centimeters seventy days later, gained weight steadily (edema and ascites were not present) and could not be distinguished from the controls on inspection.

In table 2 are presented data showing the mean weight of the entire body, heart (fresh weight, capacity of the left ventricle and weight of the separated fixed chambers) and kidney for the control animals, those on which partial nephrectomy was carried out and those which were fed thyroid.

Weight of the Animals.—The difference in weight of the control and the partially nephrectomized animals was 12 ± 5.7 Gm., which was not significant statistically. The weight of the animals which were fed thyroid was 18 per cent below that of the controls.

Kidneys.—The weights are given as the total of both kidneys for the control animals and those fed thyroid. The kidneys of the latter group weighed 47 per cent more than those of the controls, an observation repeatedly reported.

The stump of the kidney had grown until its weight was 73 per cent of that of both normal kidneys, 145 per cent of that of one normal kidney and 370 per cent of that of the original stump.

Fresh Heart.—The average weight of the fresh heart of the partially nephrectomized animals was 30 ± 4.4 mg. per hundred square centimeters heavier than that of the controls, which was a significant increase (16 per cent). The weight of the heart of the rats fed thyroid had increased 54 per cent. Before computation of the weight of the fresh left ventricle the weight of the fresh total heart was reduced by an amount calculated by the relation of the weight of the fixed atria and great vessels to the weight of the fixed total heart. Computed on the basis of a normal ratio of the weight of the left ventricle to that of the right ventricle of 2 : 47 : 1 for the animals fed thyroid and no increase in the weight of the right ventricle in the nephrectomized rats, the respective weights of the fresh left ventricles were 158 per cent and 121 per cent of the control value.

The aortas of the group with renal insufficiency were grossly thickened and more rigid than those of the controls.

Fixed Heart.—For the control group the mean crude weight of the right ventricle was 28 ± 0.9 mg. per hundred square centimeters, and the group on which partial nephrectomy had been performed, 27 ± 1.1. The difference was 1.0 ± 1.4 mg. For the control rats the mean crude weight of the left ventricle was 97 ± 1.9 mg. per hundred square centimeters; for the partially nephrectomized animals, 119 ± 2.5 mg. The difference was 22 ± 3.1, which was a significant increase. The corrected ventricular weights are shown in table 2. It may be seen that in the partially nephrectomized animals hypertrophy was entirely confined to the left ventricle, while in the animals fed thyroid, cardiac hypertrophy involved both ventricles almost equally.

The ratio of the weight of the left ventricle to that of the right was almost the same in the controls and in the rats fed thyroid (2.47 and 2.73) but had increased to 3.20 in the animals on which partial nephrectomy was performed.

TABLE 2.—*Mean Weight of the Kidneys and Heart and Mean Capacity of the Left Ventricle*

Animals	Number of Rats	Weight at Death, Gm.	Surface Area at Death, Sq. Cm.	Weight of Kidney, Mg. per 100 Sq. Cm.	Weight of Fresh Heart, Mg. per 100 Sq. Cm.		Weight of Fixed Heart, Mg. per 100 Sq. Cm.			Capacity of Left Ventricle			
					Total	Calculated, Left Ventricle	Left to Right Ratio	Corrected, Left Ventricle	Corrected, Right Ventricle	Cubic Centimeters	Cubic Millimeters per 100 Sq. Cm.	Cubic Millimeters per 100 Mg. Fresh Heart	Cubic Millimeters per 100 Mg. Fresh Left Ventricle
Controls.....	16	274±3.6	479	336	189±1.5	129	2.47	89.0	36.0	0.341	71±2.2	37±1.0	55.2
		100 %		100%	100%	100%		100%	100%	100%	100%	100%	100%
Subjected to partial nephrectomy	17	262±4.4	463	244	219±4.1	156	3.20	110.9	34.7	0.347	75±1.8	35±1.1	48.1
		96%		73 %	116 %	121%		125 %	96%	102 %	106%	95%	87%
Receiving thyroid..	7	225	420	495	291	204	2.74	142.0	52.0	0.557	133	46	65.0
		82%		147%	154%	158%		160 %	144%	163 %	187 %	124%	118%

The atria and great vessels averaged 5.6 mg. per hundred square centimeters in the control group, 9.7 mg. in the rats subjected to partial nephrectomy and 9 mg. in the animals fed thyroid.

Capacity of the Left Ventricle.—The similarity of capacity of the left ventricle in the control group and in the animals with partial nephrectomy (0.341 and 0.347 cc.) is in sharp contrast to the greatly dilated left ventricle of the animals fed thyroid (0.557 cc.). When computed on a basis of surface area the difference in capacities between the controls and the partially nephrectomized rats was $+4 \pm 2.8$ cu. mm. per hundred square centimeters; when computed on the basis of fresh heart weight, -2 ± 1.5 cu. mm. per hundred milligrams of heart. On each basis the rats fed thyroid had dilated left ventricles (+87 and +24 per cent). It may also be seen that the capacity per weight of the fresh left ventricle of the

TABLE 3.—*Changes in the Radius and Length of the Fibers Calculated from the Heart Weight and Capacity of the Left Ventricle* *

Animals	Weight of Fresh Heart, Mg. per 100 Sq. Cm.	Weight of Fresh Left Ventricle, Mg. per 100 Sq. Cm.	Capacity of Left Ventricle, Cu.Mm. per 100 Sq. Cm.	(A) Inner Surface of Left Ventricle†	(B) Radius of Fibers of Left Ventricle‡	(C) Length of Fibers (Total) of Left Ventricle§
Control.....	189 100%	129 100%	71 100%	100%	100%	100%
Subjected to partial nephrectomy	219 116%	156 121%	75 106%	104%	116%	90%
Receiving thyroid..	291 154%	204 158%	133 187%	152%	104%	146%

* The calculations are based on the data reported in the paper. The close agreement of calculations based on our observations with those based on Chanutin's observations may be seen by comparing these data with those in table 1. Note the markedly different findings in the group that had been fed thyroid.

† This is calculated by taking the 2/3 power of the capacity of the left ventricle and expressing it as percentage of the control value.

‡ This is the quotient of $\frac{\text{left ventricular weight}}{\text{left ventricular inner surface}}$, each expressed as percentage of the control value.

§ This is determined by dividing the figure in column A by that in column B. (Since the ventricular weight varies as the product of the fiber length times the radius squared, and the inner surface of the ventricle varies as the fiber length times the radius, then $\frac{\text{weight}}{\text{surface}} = \text{radius}$, and $\frac{\text{surface}}{\text{radius}} = \text{length}$.)

animals with renal insufficiency actually diminished 13 per cent of that of the controls, while that of the rat fed thyroid increased 18 per cent.

In brief, the heart of the rat made hypertensive by deprivation of renal tissue reacts by an increase in the weight of its left ventricle alone, while the cavity of the left ventricle not only does not dilate but is relatively small in comparison to the weight of its surrounding myocardium. On the other hand, the heart of the rat fed thyroid becomes heavier in both ventricles equally, while the dilatation of the left ventricle closely parallels hypertrophy.

In table 1 calculations of the length of fibers and capacity of the left ventricle were made from Chanutin's data on the weight of the heart and the measured width of the fibers. In table 3 are shown

calculations of the width and length of fibers of the left ventricle based on the weight of the heart and measured capacity. The two sets of data are in close agreement and complement each other.

The data in table 3 again emphasize the distinction between the two mechanisms of hypertrophy; the myocardial fibers of the left ventricle of the rats fed thyroid were found to gain only 4 per cent in width but 46 per cent in length, while the fibers of the hypertensive rats were 16 per cent wider and 10 per cent shorter.

COMMENT

Many pathologists doubt and most physiologists deny the existence of cardiac hypertrophy without an increase in the capacity of the ventricles. In discussing this problem, some define concentric hypertrophy as an increase in weight with a decrease in the capacity of the chamber; others, as an increase in weight with unchanged capacity, and a few, as an increase in weight with relatively little increase in capacity. We use the term in the sense of increased weight without an increase in capacity, as distinguished from eccentric hypertrophy in which capacity as well as weight is increased. That is, in concentric hypertrophy there must be a decrease in the ratio of capacity to weight; in dilatation there is an increase in capacity without an increase in weight, and in eccentric hypertrophy the increase in weight and capacity are parallel, or there is a rise in the ratio of capacity to weight.

Concentric hypertrophy of a ventricle is an increase in the volume and weight of its myocardial fibers caused by an increase in the width of the fibers; it is associated with a relatively small ventricular cavity, no significant increase in capacity per unit of body surface area and a shortening of the total length of the fibers. Eccentric hypertrophy, on the other hand, implies a parallel increase in the volume of the cavity and in the wall of the ventricle, the latter mediated by lengthening of the myocardial fibers.

Disregarding definition, Krehl [5] and Fishberg,[6] with many clinicians, have accepted concentric hypertrophy as the usual course of events in a person with hypertension whose heart has not failed. Adami [7] denied the existence of concentric hypertrophy on theoretical physiologic grounds and explained the reported instances as artefacts due to rigor

5. Krehl, L.: The Principles of Clinical Pathology, translated by A. W. Hewlett, ed. 2, Philadelphia, J. B. Lippincott Company, 1907, p. 60.

6. Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1931, p. 170.

7. Adami, J. G.: Notes upon Cardiac Hypertrophy, Montreal M. J. **23**:811 (May) 1895.

mortis. Kaufmann [8] noted the condition rarely, and Mönckeberg [9] photographed it. Dietlen [10] urged that the term be dropped as the conception was in conflict with physiologic tenets and the condition impossible of existence.

There has been a striking absence of actual data concerning concentric hypertrophy. Two hundred years ago Stephen Hales [11] poured melted yellow wax into the left ventricles of animals and used the resulting values for volume and inner surface area of the ventricles in his computations on the work of the heart. Since then, there have apparently been only two workers who seriously studied ventricular volume in relation to hypertrophy.

Du Castel [12] measured the capacities of both ventricles in the hearts of 62 persons dying of various ailments and found in at least 1 instance *la véritable hypertrophie concentrique*. Widerøe [13] investigated the weight and capacity of both ventricles in 311 cases; he reported his results and reviewed the literature on the size of the heart in an extensive monograph. On the average, in 9 cases of chronic nephritis the ratio of the weight of the left ventricle to the body weight increased 100 per cent above that of the controls; the ratio of the weight of the right ventricle to the body weight increased 57 per cent, and the ratio of the capacity of the left ventricle to that of the right ventricle increased 51 per cent. The data of both authors are complicated by the heterogeneity of their series and by the necessity of including cases of heart failure, so that the bearing of the data on the existence of concentric hypertrophy is questionable. By the use of experimental animals killed at will and with different methods of obtaining data, both Chanutin and we have shown that when there is renal insufficiency the heart of a rat reacts to hypertension with unquestionable concentric hypertrophy of the left ventricle.

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8. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 73.

9. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 350.

10. Dietlen, Hans: Herzgrösse, Herzmessmethoden; Anpassung, Hypertrophie, Dilatation, Tonus des Herzens, in Bethe, A.; Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, p. 351.

11. Hales, Stephen: Statical Essays, London, W. Innys and others, 1733.

12. du Castel: Recherches sur l'hypertrophie et la dilatation des ventricules du cœur, Arch. gén. de méd. **145**:25, 1880.

13. Widerøe, Sofus: Die Massenverhältnisse des Herzens unter pathologischen Zuständen, Christiania, Jacob Dybwad, 1911.

Current physiologic teaching [14] holds that the heart responds to demands for added work by dilatation (lengthening of the fibers), for, according to Starling's "law of the heart," the energy of contraction is a function of the length of the muscle fibers. If the demand for increased work continues the dilated heart becomes hypertrophied (the stretched fibers increase in width). It has been largely on the authority of Starling's law that the existence of concentric hypertrophy has been denied.

However, an important point in cardiodynamics first raised by Patterson and Starling and amplified by Gesell has been neglected. The former authors [15] stated:

> If the cavity of each ventricle were perfectly spherical the tension on each muscle fiber would be greater the greater the capacity of the sphere, assuming the intracardiac pressure to remain constant. (The total pressure on the whole of the boundary layer of a sphere will vary as its surface and therefore as the square of the radius. While the length of each muscle fiber lying in the circumference of the sphere would vary directly as the radius, the amount of fluid to be forced out by a given shortening of the muscle fibers would vary as the cube of the radius.) Since under normal conditions the capacity of the heart cavities becomes less during the contraction of the ventricle, a constant tension on the muscle fibers would tend to produce a pressure in the heart cavities which would increase steadily as the emptying proceeded and their capacity became smaller. . . . It may be remembered that . . . most skeletal muscles contract in this way, since they act at a greater mechanical advantage . . . when contracted than when commencing their contraction.

Gesell [16] made an extensive mathematical study of the surface-volume relation and showed that "the efficiency of the contractile energy increases more rapidly per unit of muscle shortening the smaller the initial volume, a factor which would point to an optimum initial volume for maximum utilization of contractile energy."

In a ventricle with constant contractile energy a given unit of shortening of the muscle fibers will expel a comparatively large volume (at relatively low pressure) if the initial capacity is great, while the same amount of shortening will develop a greater endocardiac pressure the smaller the initial capacity (with a smaller stroke output). Viewed in this light, the contrasting mechanisms of hypertrophy exhibited by the heart of the rat with hypertension (concentric) and that of the rat with hyperthyroidism (eccentric) are readily understood.

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14. Starling, E. H.: Principles of Human Physiology, ed. 6, revised by C. L. Evans, Philadelphia, Lea & Febiger, 1933, p. 773.

15. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, J. Physiol. **48**:357 (Sept. 8) 1914.

16. Gesell, Robert A.: Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve, Am. J. Physiol. **40**:267 (April 1) 1916.

The optimal initial size of the heart of a subject with hyperthyroidism, which must expel an increased minute output against presumably normal peripheral resistance, should obviously be greater (in both chambers) than that of the heart of a subject with hypertension, which must expel a normal minute output against an increased peripheral resistance in the systemic circuit. As a matter of fact, the heart of a subject with hyperthyroidism does present parallel increases in myocardial weight and ventricular capacities, while the fibers of the left ventricle of the heart of the hypertensive subject grow wider and shorter. When hypertension develops gradually it is unlikely that dilatation of the heart occurs at any time; hypertrophy in such cases at least is not preceded by lengthening of the fibers. We have, however, no actual data on the diastolic volume in vivo.

CONCLUSIONS

1. The heart of the rat reacts to the arterial hypertension of renal insufficiency by the production of concentric hypertrophy of the left ventricle.

2. In concentric hypertrophy so induced, the myocardial fibers of the left ventricle are increased in width and decreased in length.

3. The heart of the rat reacts to artificial hyperthyroidism by the production of eccentric hypertrophy involving the two ventricles equally.

4. In eccentric hypertrophy so induced, the myocardial fibers do not show a significant change in width but lengthen greatly.

5. A consideration of cardiodynamics shows that concentric hypertrophy is the optimum compensatory mechanism for the heart of the subject with hypertension and eccentric hypertrophy for the heart of the subject with hyperthyroidism.

SUMMARY

With a modification of Chanutin's technic for bringing about renal insufficiency, cardiac hypertrophy was produced in a group of albino rats; the hearts were compared with normal hearts and with hearts with hypertrophy induced by the feeding of thyroid. Our results were shown to confirm and extend those of Chanutin. The findings were discussed in relation to cardiodynamic principles.

STUDIES OF HEPATIC FUNCTION

II. IN PORTAL CIRRHOSIS AND CONGESTIVE HEART FAILURE

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No one can gainsay the inadequacy, in many respects, of present-day methods of investigating the functional efficiency of the liver. General recognition of this fact apparently has led to the feeling among many clinicians that little information can be obtained by these methods. As a result, little or no attempt is made to determine the state of hepatic function in many clinics in which elaborate studies of renal function, for example, may be a matter of routine. My experience in this field has convinced me of the value of a careful and detailed study of hepatic function by readily available methods in a great variety of clinical disorders, and it has led to the belief that much of the discredit which is attached to these procedures is due to errors of interpretation rather than to faults inherent in the methods.

The present report consists of observations made on patients with portal cirrhosis, Banti's disease and congestive heart failure. The bilirubin content of the serum was determined by the quantitative van den Bergh method as modified by Thannhauser and Andersen. As stated in a previous report,[1] the normal range of serum bilirubin, in my experience, is from 0.1 to 1.0 mg. per hundred cubic centimeters, the value in 50 per cent of cases falling below 0.5 mg. per hundred cubic centimeters and in 95 per cent, below 0.8 mg. Bromsulphalein was injected in a dosage of 2 mg. per kilogram, and a single determination was made at the end of thirty minutes. The cholesterol content of the plasma was determined by the method of Myers and Wardell as modified by Oser and Karr,[2] and the amount of urobilinogen in the urine, by the method of Wallace and Diamond.[3]

PORTAL CIRRHOSIS

There were twenty-two patients with portal cirrhosis. The detailed data are presented in table 1. It will be noted that normal findings were

From the Laboratory of Biochemistry and the Department of Medicine, Jefferson Hospital.

1. Cantarow, A.: Studies of Hepatic Function: I. Noncalculous and Calculous Cholecystitis, Arch. Int. Med. **54**:540 (Oct.) 1934.

2. Oser, B., and Karr, W. G.: The Lipoid Partition in Blood in Health and in Disease, Arch. Int. Med. **36**:507 (Oct.) 1925.

3. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

obtained in only four (18.1 per cent) cases in this series. Visible jaundice was present in eight instances (cases 1 [not on admission], 2, 5, 6, 7, 9, 12 and 15), although hyperbilirubinemia was present in three others and also in case 1 at the time of admission. Of the seven normal values for serum bilirubin, three were between 0.9 and 1 mg., figures which would be obtained in less than 5 per cent of normal persons. This observation in itself indicates the importance of the routine determination of the serum bilirubin concentration in cases of suspected hepatic dysfunction and the unreliability of clinical observa-

TABLE 1.—*Data on Cases of Portal Cirrhosis*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Brom-sulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Uro-bilinogen in the Urine	Ascites
1	6/ 3/32	0	1.2	0	...	1:20	..
	6/19/32	+	2.4	0	....	....	0
	10/ 5/32	+	3.0	20	100	....	..
	11/16/32	+	6.4	20	...	....	..
2	.....	+	3.8	0	...	1:20	+
3	.....	0	1.1	10	...	....	0
4	11/23/32	0	1.2	40	164	1:300	..
	12/ 8/32	0	1.6	60	...	.....	0
5	.....	+	6.0	40	162	.....	+
6	.....	+	3.7	40	200	1:200	+
7	.....	+	2.4	40	...	.....	+
8	.....	0	0.4	10	...	.....	0
9	.....	+	4.0	80	131	1:20	+
10	1/ 3/33	0	0.92	25	119	....	..
	1/26/33	0	0.92	60	...	....	0
11	.....	0	1.0	5	131	1:10	0
12	.....	+	2.43	55	158	1:50	0
13	.....	0	0.48	10	100	1:40	0
14	.....	0	1.0	40	211	1:200	0
15	.....	+	8.2	35	...	1:400	+
16	.....	0	0.63	10	186	1:100	0
17	.....	+	1.5	25	...	....	0
18	.....	0	0.55	10	...	1:50	0
4 cases.....			0.34-0.91	0	126-164	1:10-1:40	0

tion in the detection of early or latent jaundice, a fact which is generally recognized.

Rolleston and McNee [4] stated that jaundice is not a prominent feature of portal cirrhosis but that it occurs in more than one third of the cases at some time during the course of the disease. They reported that jaundice was present in 36.5 per cent of a collected series of 293 cases. It has been found [5] to be present in only 8 per cent of

4. Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gall Bladder and Bile Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 258.

5. Diseases of Metabolism and of the Digestive Tract, Vienna letter, J. A. M. A. **85**:1573 (Nov. 14) 1925.

ninety cases of portal cirrhosis. Nissen [6] noted icterus in sixty-two of seventy-seven cases post mortem, when pigmentation of the skin is more evident than during life, and Chapman, Snell and Rowntree [7] reported its presence in forty-three (38.4 per cent) of 112 cases of the late stages of the disease. All are agreed that jaundice is usually absent in the preascitic stage, although slight grades of hyperbilirubinemia have been observed during this period by Diamond,[8] by Gilbert, Herscher and Posternack [9] and by Greene, McVicar, Snell and Rowntree.[10] In the present series, ascites was demonstrable in cases 2, 5, 6, 7, 9 and 15, with serum bilirubin values ranging from 2.4 to 8.2 mg. per hundred cubic centimeters. No ascites was present (at autopsy) in case 1, in which the serum bilirubin concentration was 6.4 mg. However, there seems little question that in the absence of such complicating factors as cholangeitis, cholelithiasis and duodenitis the higher values are obtained in the more advanced stages of the cirrhotic process. It is of interest to note in this connection, however, that ascites may in some instances be in part dependent on factors other than cirrhosis, e. g., chronic peritonitis or perihepatitis, and may not indicate accurately the severity of the cirrhotic process. For example, of the seventy-seven patients studied at autopsy by Nissen,[6] forty-four presented both jaundice and ascites, eighteen jaundice without ascites and fifteen ascites without jaundice. It is evident that whereas in the experience of the majority of observers ascites usually precedes the development of visible icterus, this is not invariably the case, and varying degrees of hyperbilirubinemia may be present in many cases before ascites can be demonstrated.

The direct van den Bergh reaction was positive in every instance in this series in which the serum bilirubin was above 2 mg. per hundred cubic centimeters and was negative in every case in which the value was below this figure, with one exception (case 17, 1.5 mg.). A positive direct reaction in portal cirrhosis may be due to extensive hepatic necrosis or to intrahepatic canalicular or extrahepatic ductal obstruction. As pointed out by Althausen,[11] the newly formed hyperplastic nodules

6. Nissen, H. A.: Cirrhosis of the Liver Showing Jaundice and Ascites, M. Clin. North America **4**:555, 1920.

7. Chapman, C. B.; Snell, A. M., and Rowntree, L. G.: Decompensated Portal Cirrhosis, J. A. M. A. **97**:237 (July 25) 1931.

8. Diamond, J. S.: The Value of Routine Estimations of Blood Bilirubin, Am. J. M. Sc. **176**:321, 1928.

9. Gilbert, A.; Herscher, M., and Posternack, S.: Sur la signification de l'anneau bleu produit par le réactif de Gmelin dans certains sérums, Compt. rend. Soc. de biol. **55**:584, 1903.

10. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Diseases of the Liver: VI. A Comparative Study of Certain Tests for Hepatic Function in Cases of Cirrhosis of the Liver, Arch. Int. Med. **40**:159 (Aug.) 1927.

11. Althausen, T. L.: Functional Aspects of Regenerated Hepatic Tissue, Arch. Int. Med. **48**:667 (Oct.) 1931.

frequently lack connection with bile channels, which may account in part for the development of a regurgitation (Rich) type of hyperbilirubinemia in the later stages of the disease. A positive direct reaction has been reported in patients with portal cirrhosis by Greene, McVicar, Snell and Rowntree,[10] by Cabot,[12] by Comfort and Snell,[13] by Barker[14] and by Shattuck, Browne and Preston.[15] A positive direct reaction was obtained by Barker[14] with a serum bilirubin concentration as low as 1 mg. per hundred cubic centimeters, and, on the other hand, Comfort and Snell[13] reported a negative direct reaction in one case with a serum bilirubin concentration of 3.3 mg. per hundred cubic centimeters.

Some degree of retention of bromsulphalein was present in seventeen (77.3 per cent) of the twenty-two cases in this series, although no retention was noted in case 1 at the time of admission. Cases 1 and 2 are only instances, in the present series, of hyperbilirubinemia without retention of dye, whereas the reverse, retention of dye (from 5 to 60 per cent) without hyperbilirubinemia, was noted in seven cases (cases 8, 10, 11, 13, 14, 16 and 18). It is evident that bromsulphalein retention can be demonstrated frequently in early stages of portal cirrhosis before hyperbilirubinemia has developed. Some degree of dye retention was noted in eighty of eighty-seven cases reported by Chapman, Snell and Rowntree.[7] Other reports are as follows: Cabot,[12] from 45 to 70 per cent; Barker,[14] slight retention; Eusterman,[16] slight retention; Piersol and Rothman,[17] from 0 to 20 per cent; Epstein,[18] from 0 to 25 per cent; O'Leary, Greene and Rowntree,[19] from 2 to 40 per cent; Robertson, Swalm and Konzelmann,[20] from 2 to 30 per cent; Foley,[21]

12. Cabot, R. C.: Case Records of the Massachusetts General Hospital, New England J. Med. **205**:107, 222 and 1056, 1931.

13. Comfort, M. W., and Snell, A. M.: Treatment of Portal Cirrhosis, M. Clin. North America **15**:107, 1931.

14. Barker, L. F.: Presentation of Cases of Portal Cirrhosis, M. Clin. North America **14**:87 and 99, 1930.

15. Shattuck, H. F.; Browne, J. C., and Preston, M.: Clinical Value of Some Recent Tests for Liver Function, Am. J. M. Sc. **170**:510, 1925.

16. Eusterman, G. B.: Errors in the Diagnosis of Diseases Associated with Jaundice, Ann. Int. Med. **6**:608, 1932.

17. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

18. Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82 (Jan.) 1931.

19. O'Leary, P. A.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: VIII. The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function, Arch. Int. Med. **44**:155 (Aug.) 1929.

20. Robertson, W. E.; Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver: Comparative Merits of the Five Most Popular Tests, J. A. M. A. **99**:2071 (Dec. 17) 1932.

21. Foley, E. F.: The Clinical Value of Tests of Liver Function, Arch. Int. Med. **45**:302 (Feb.) 1930.

from 5 to 30 per cent; Shattuck, Browne and Preston,[15] from 0 to 16 per cent. Greene, McVicar, Snell and Rowntree[10] found retention of from 0 to 35 per cent in patients with ascites and a contracted liver, from 5 to 28 per cent in those with ascites and an enlarged liver and from 0 to 11 per cent in those without ascites. In the present series it is apparent that the relationship between the degree of retention of dye and the presence of ascites is not nearly as consistent as is the relation of the latter to the degree of hyperbilirubinemia.

As was noted in previously reported studies of hepatic function in cases of cholecystitis,[22] the absence of a consistent correlation between the degree of retention of bromsulphalein and the concentration of serum bilirubin is of distinct practical value as well as of theoretical significance in evaluating the relative significance of obstructive and nonobstructive factors in the mechanism of production of the existing disturbance of hepatic excretory function. Although the higher grades of retention of dye are frequently found to be associated with the higher levels of bilirubinemia, this relationship is by no means invariable in portal cirrhosis. For example, in case 1, the retention of dye remained at 20 per cent while the concentration of serum bilirubin rose from 3 to 6.4 mg. per hundred cubic centimeters; in case 2 there was no retention of dye with a serum bilirubin concentration of 3.8 mg. per hundred cubic centimeters. Cases 8, 10, 13, 16 and 18 also illustrate the dissociation of these two phases of the excretory function of the liver. Such findings are not obtained in conditions in which an obstructive mechanism is operative, except during periods following relief of obstruction, such as after passage or removal of a stone from the common bile duct.

There is considerable difference of opinion regarding the pathogenesis of hyperbilirubinemia in portal cirrhosis. Rich[23] placed this condition in the category of "regurgitation" jaundice, due to necrosis of hepatic cells, which occurs in the late stages of the disease. Other observers attribute this phenomenon to radicular cholangeitis, to cholangeitis of the larger ducts, to duodenitis and even to compression and kinking of the extrahepatic ducts. As mentioned before, Althausen[11] stated the belief that the regurgitation type of hyperbilirubinemia in the later stages may be due to the fact that the newly formed hyperplastic nodules frequently lack connection with bile channels. In view of the frequent occurrence of dissociation of the bilirubin concentration and the retention of bromsulphalein, it appears likely that primary impair-

22. Cantarow, A.: The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, Am. J. M. Sc. **184**:228, 1932; footnote 1.

23. Rich, A. R.: The Pathogenesis of Jaundice, Bull. Johns Hopkins Hosp. **47**:338, 1930.

ment of the function of the hepatic cells plays a much more important part than any obstructive mechanism in the production of hyperbilirubinemia in portal cirrhosis. The presence of excessive urobilinuria in many cases and the occasionally subnormal concentration of plasma cholesterol (cases 1, 9, 10, 11 and 13) add further support to this view.

BANTI'S DISEASE

Observations made on four patients with splenic anemia in whose cases the diagnosis of Banti's disease was made are presented in table 2. Advanced hepatic involvement, with ascites, was present in cases 2 and 3. What has been said regarding the findings in portal cirrhosis applies equally here. It may be noted that in case 4 a negative direct van den Bergh reaction and normal excretion of bromsulphalein were present in association with a serum bilirubin concentration of 2.7 mg. per hundred cubic centimeters.

TABLE 2.—*Data on Cases of Banti's Disease*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Bromsulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Urobilinogen in the Urine
1	.....	+	1.5	20	...	1:60
2	.....	+	6.0	60	162	1:100
3	.....	+	3.6	30	...	1:200
4	6/27/33	0	2.7	0	147	1:100
Splenectomy	7/15/33					
	7/15/33	0	1.5	0	...	.....
	9/20/33	0	0.8	..	...	1:20

CONGESTIVE HEART FAILURE

Data were obtained in forty-two cases of congestive heart failure of varying degree. These are presented in detail in table 3. Abnormal findings were obtained in fourteen cases (33 per cent). No attempt is made to classify these according to the nature of the underlying lesions and of the degree of pulmonary and hepatic involvement, obviously factors of great importance in this connection.

Visible jaundice was noted in only two patients (cases 7 and 12), although some degree of hyperbilirubinemia was present in eight additional patients. In view of the significance of this phenomenon in patients with congestive heart failure, this observation emphasizes the importance of the determination of the serum bilirubin concentration and the unreliability of the clinical recognition of jaundice of relatively mild degree. As pointed out by Fishberg,[24] a state of latent or mild icterus in such patients is frequently masked by cyanosis. Foley [21]

24. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80**: 1516 (May 26) 1923.

reported serum bilirubin values ranging from 0.4 to 7.7 mg. per hundred cubic centimeters in a group of thirty patients with chronic passive congestion of the liver, visible jaundice being noted in eleven. Andrewes [25] obtained values ranging from 0.4 to 7.5 van den Bergh units (0.16 to 3 mg. per hundred cubic centimeters) in fourteen patients with cardiac disease. He stated that patients without gross failure all gave a normal result while those with gross failure, especially with enlarged livers, usually had latent if not obvious jaundice; hepatic enlargement and hyperbilirubinemia did not always go hand in hand. Kugel and Lichtman,[26] in a study of fifteen cases of "cardiac" jaundice, reported values for serum bilirubin ranging from 0.5 to 8 mg. per

TABLE 3.—*Data on Cases of Congestive Heart Failure*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Brom-sulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Uro-bilinogen in the Urine	Edema
1	6/ 1/32	0	0.76	5	...	....	..
	7/14/32	0	1.48	40	...	1:40	+++
2	.....	+	1.5	10	...	....	+
3	.....	0	1.25	15	212	....	+
4	.....	0	0.37	5	...	....	+
5	.....	+	1.5	40	188	1:10	++
6	.....	0	0.7	10	...	....	+
7	.....	+	4.1	30	118	1:60	+++
8	.....	0	1.0	10	...	....	++
9	11/10/32	0	1.89	25	...	....	++
	12/ 2/32	0	1.2	0	...	....	+
10	11/21/32	0	1.68	60	...	....	++
	11/25/32	0	1.8	40	...	....	..
	12/ 5/32	0	0.84	40	...	1:30	++
11	.....	+	2.6	20	164	....	+
12	.....	+	3.0	100	...	1:40	++
13	.....	0	1.2	10	...	....	+
14	.....	0	0.63	100	172	....	+++
28 cases.....			0.12-0.94	0	126-206	0-1:20	+ to +++

hundred cubic centimeters, the content being above 2 mg. in twelve instances. A prompt direct van den Bergh reaction was obtained in ten of eleven cases in which this test was performed. This reaction was obtained in only five of the ten patients with hyperbilirubinemia in the present series. In Jolliffe's [27] series of sixteen patients, not all of whom were visibly jaundiced, 93 per cent showed some laboratory evidence of impaired function of the liver although in only one instance were the results of all tests employed abnormal.

25. Andrewes, C. H.: A Clinical Study of van den Bergh's Test in Jaundice, Quart. J. Med. **18**:19, 1924.

26. Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease, Arch. Int. Med. **52**:16 (July) 1933.

27. Jolliffe, N.: Liver Function in Congestive Heart Failure, J. Clin. Investigation **8**:419, 1930.

There is no unanimity of opinion regarding the pathogenesis of hyperbilirubinemia in patients with congestive heart failure. The two major opposing concepts stress the fundamental importance, respectively, of (1) hepatic functional impairment and (2) formation of excess bilirubin from hemoglobin liberated from areas of pulmonary infarction. Fishberg [24] explained the development of jaundice on the basis of two factors: (1) increased destruction of stagnated red blood cells by cells of the reticulo-endothelial system (liver, lungs, spleen); (2) impaired excretion of bilirubin by the liver as a result of injury of hepatic cells incident to chronic passive congestion. Rich,[23] Rosin,[28] Campbell [29] and others demonstrated the effect of anoxemia in producing atrophy of cells about the efferent veins of the hepatic lobules, and Rich and most subsequent observers have expressed the belief that this factor is the basis of the characteristic changes in the hepatic cells present in cases of myocardial failure. Rich,[23] however, stated the belief that jaundice does not occur in the presence of anoxemia unless there is a simultaneous overproduction of bilirubin. According to Barron,[30] in the great majority of instances this form of hyperbilirubinemia is of the retention type, with a negative direct van den Bergh reaction; aggravation of the existing state of anoxemia by the development of pulmonary infarction, as shown by Binger, Brow and Branch,[31] may convert latent into visible jaundice. As the condition progresses and damage to the hepatic cells increases, actual necrosis may occur, "regurgitation" jaundice develop and a positive direct van den Bergh reaction be obtained.

Kugel and Lichtman [26] expressed an inclination toward the opposite view on the basis of their clinical and morphologic study of a rather large series of bases. Their concept is as follows: Bilirubin is formed from hemoglobin liberated from areas of pulmonary infarction and is absorbed into the circulation. The excretory capacity of the liver is impaired because of anoxemia and, in some cases, infection. However, unless extensive hepatic disease is present, i. e., true cirrhosis, the jaundice is primarily pulmonogenic, the deleterious effects of anoxemia being of secondary importance.

The data reported here throw no light on this problem. It is of interest, however, to note again the absence of correlation between the degree of retention of bromsulphalein and that of bilirubinemia in several instances. The severity of the condition of myocardial failure

28. Rosin, A.: Morphologische Organveränderungen beim Leben unter Luftverdünnung, Beitr. z. path. Anat. u. z. allg. Path. **80**:622, 1928.

29. Campbell, J. A.: Concerning the Problem of Mount Everest, Lancet **2**:84, 1928.

30. Barron, E. S. G.: Bilirubinemia, Medicine **10**:77, 1931.

31. Binger, C. A.; Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing: I and II, J. Clin. Investigation **1**:127 and 155, 1924.

appeared to be more consistently related to the degree of retention of dye than to the concentration of serum bilirubin (e. g., cases 10 and 14) in the cases in which abnormal findings were obtained. These observations suggest that hepatic functional impairment, as indicated by retention of dye, is present in practically all cases with hyperbilirubinemia but that marked impairment of excretion of dye may be present without hyperbilirubinemia. Whether the latter observation may be interpreted as evidence that jaundice in cases of congestive heart failure is not primarily dependent on hepatic functional impairment is a question which cannot be answered until more is known regarding the exact method and path of excretion of bromsulphalein by the liver and what relation it bears to the excretion of bilirubin.

SUMMARY

Hyperbilirubinemia or abnormal retention of bromsulphalein or both were present in seventeen of twenty-two patients with portal cirrhosis. Visible jaundice was present in eight of twelve patients with hyperbilirubinemia.

Although ascites usually precedes the development of visible icterus, varying degrees of hyperbilirubinemia may be present in many cases before ascites can be demonstrated.

Retention of bromsulphalein was noted in 77.3 per cent of the cases in this series, being at times exhibited by patients with normal serum bilirubin values (seven cases). The relationship between retention of dye and the presence of ascites was not as consistent as was the relation of the latter to the degree of hyperbilirubinemia.

This dissociation of the retention of dye and that of bilirubin is practically never encountered in obstructive types of hyperbilirubinemia and suggests that primary impairment of the function of the hepatic cells is of fundamental importance in the production of hyperbilirubinemia in cases of portal cirrhosis. Similar observations were made in four cases of splenic anemia (Banti's disease).

Hyperbilirubinemia was present in ten of forty-two cases of congestive heart failure, in only two of which there was visible jaundice. Abnormal retention of bromsulphalein was present in fourteen cases. The severity of the condition appeared to be more consistently related to the degree of retention of dye than to the concentration of serum bilirubin.

Marked impairment of excretion of dye may occur in the absence of hyperbilirubinemia. Although not conclusive, this observation suggests that some factor, probably pulmonary infarction, other than hepatic functional impairment is necessary for the production of hyperbilirubinemia in patients with congestive heart failure.

Progress in Internal Medicine

PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE WITH A CRITICAL REVIEW OF SURGICAL TREATMENT

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A REVIEW OF SOME OF THE RECENT LITERATURE

By Dr. Scupham

The advances which have been made both in the understanding of the diseases of the blood vessels of the extremities and in their treatment are an example of what can be accomplished when interest is widely aroused in a particular subject.

This interest not only has resulted in increased information concerning the diseases in question but has given rise to increased knowledge of the physiology of the autonomic nervous system and its relation to the circulation, as well as of the function, normal and abnormal, of so important a group of vessels as the capillaries. Earlier observations have been subjected to critical analysis with clarification of the concepts. Just as all diseases of the blood vessels were at one time included under the term arteriosclerosis and the inflammatory and spasmodic varieties, embolism and thrombosis, split off, so further clarification of the present classifications is being sought. The problems are by no means solved, but important advances have been made.

The diagnosis of vascular disease is now being made in a relatively early stage, whereas only a short time ago such a condition continued almost invariably to gangrene and amputation of the extremity at a high level or loss of life. The advances in treatment have been as important as the progress in the means of diagnosis.

Not only in diseases of the arteries of the extremities has the better understanding of the physiopathologic processes involving the

blood vessels become apparent, but recent studies on these vessels have given increased insight into some of the more obscure types of visceral vascular diseases.

The initial advances were the result of detailed observation and study of individual cases; the later one represented the development of new methods and apparatus as well as the application of physiologic experiments to the study of the circulation.

Riesman [1] has recently commented on the rapid development of interest in the study of vascular diseases to the point of specialization. This enthusiasm has advanced the knowledge, but the danger of limitation to too narrow a field is obvious. Vascular diseases must be approached from the standpoint of medicine as a whole. They cannot be limited to any field, as the problems are pertinent to all branches.

This review is by no means inclusive of all the publications on the subject, nor is the bibliography complete. In the attempt to make the subject somewhat less confusing than it might otherwise be, the study has been extended back for five years or more, and certain papers have been selected because they are representative of a special type of work or include or confirm the reports of others on the same subject. In order to keep within the limitations of space, the same procedure has been applied to the more recent contributions.

THE CAPILLARY CIRCULATION

There has been much variation of opinion in regard to both the structure of the capillaries and their reactions. This disagreement is the result, in part at least, of interpretations based on observations on specimens preserved by fixation or injection, and the minute and delicate structure of these vessels may be much altered from their normal character in living persons. The many careful studies on living amphibians and mammals have resulted in a great increase in the knowledge, but the variations which occur in different species as well as in different structures of the same animal make the application of these observations to man uncertain.

Newer methods for the study of the living capillaries in man have begun to clarify the knowledge previously gained and have made distinct additions to it. The application of photography [2] to the observation of the vessels in the nail fold by means of the capillary microscope is now a satisfactory procedure for obtaining permanent records for comparison.

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1. Riesman, David: Vascular Crises, Ann. Int. Med. **8**:1047 (March) 1935.
2. Duryee, A. W., and Wright, I. S.: Present Day Technique for the Study of Human Capillaries, Am. J. M. Sc. **185**:664 (May) 1933.

The wall of a capillary [3] consists of an inner endothelial layer and an apparent outer muscular layer. This muscular layer is not continuous but consists of a network of fine fibrils which connect with the Rouget cells. These cells and fibrils make up the contractile system of the capillaries. The presence of these cells in man has been questioned, but Wright is of the opinion that Rouget cells or their counterpart exist.

Kuntz [4] states:

> That the capillary vessels are functionally innervated is quite generally conceded both by reason of observed anatomical relationship of nerve fibers to the capillaries and by reason of the physiological behavior of the capillaries under normal and experimental conditions. The data available at present, however, do not warrant the conclusion that all capillaries are directly innervated.

Krogh [5] is of the opinion that if the existence of Rouget cells constituting a muscular coat is accepted, innervation by the sympathetic nervous system is to be expected. This he believes to have sufficient basis of fact.

The conception of a passive rôle for the capillaries in regard to the flow of blood through them is no longer tenable. Landis [6] states:

> Krogh and Lewis have summarized an impressive mass of evidence showing that the capillary vessels are independently contractile and capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissue.

Apparently Krogh [5] is of the opinion that independent contractility is of the greatest importance to the regulation of blood flow, admitting that arteriolar in-flow and increase in venous pressure do affect the balance but that contractility is capable of overcoming any possible increase in pressure from these causes.

Duryee and Wright attempted to obtain a definite impression of the flow of blood through these vessels. To do so they employed a "two minute flow test." The capillary is observed under the microscope, and the number of seconds of stoppage and flow are noted. Under average normal conditions the blood will cease to flow after from ten to twenty seconds of the two minute period.

Landis has directly measured capillary pressure [6] in both the arteriolar and the venous capillary limbs. He has found that the fall

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3. Wright, I. S., and Duryee, A. W.: The Human Capillaries in Health and Disease, Arch. Int. Med. **52**:545 (Oct.) 1933.

4. Kuntz, Albert: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1934.

5. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1929.

6. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:3 (July) 1934.

in pressure does not cease at the arteriolar junction but continues through the capillary network and under conditions of arteriolar dilatation may even extend to the venules. From 20 to 30 per cent of the peripheral resistance to blood flow is located in the capillaries. The pressure decreases slightly in the larger arteries; the gradient is steepest in the arterioles but continues through the capillaries. By his method of microcannulation Landis has found the average pressure in the arteriolar capillaries of the nail fold in man to be 43.5 cm. of water with a pressure of 16.5 cm. of water in the venous capillary. This method requires a skill and technic which prohibit its use as a routine measure. The Danzer and Hooker indirect method is considered suitable by Duryee and Wright.[2]

Capillary pressure is an extremely variable quantity, varying from moment to moment in the same and different vessels. Arteriolar constriction increases peripheral resistance, and capillary pressure falls. It rises during hyperemia caused by heat, and in the presence of histamine and acute inflammation. Under these conditions the observed blood flow becomes more rapid, and pulsations become apparent with an increase in pulse pressure. It is interesting to note that in persons with Raynaud's disease the capillary pressure was found to be below 7 or 8 mm. of mercury during the paroxysm with a very small pulse pressure, but during the phase of relaxation Landis found that it might rise to 40 mm. of mercury with a very high pulse pressure.

According to these observations the relation of blood pressure in the capillaries to the rate of flow is often very close, and the rhythmic increase with cardiac systole may penetrate to the venous capillaries. Cold first diminishes the pressure, which later rises with reactive hyperemia.

Another factor which affects the pressure in the capillaries is the obstruction to outflow offered by an increase in venous pressure. It is higher in dependent portions of the body owing to the hydrostatic pressure of vertically located veins. It is most constant in the hand when it is above the level of the base of the heart and higher when the hand is below that level.

In regard to the interpretation of observations on the moving column of cells in the capillaries with projected light, by means of which the walls of these minute vessels are not visible, Krogh [5] cautions against the repeated errors made by interpreting gaps in the column of cells and overfilled portions of the vessel as peristaltic waves. He comments on the fact that the "theories in regard to 'peripheral hearts' have been cropping up again and again and are even now seriously discussed and refuted." Wright and Duryee [3] are in agreement with Kling-Müller on this point, that the so-called peristaltic waves in the capillaries are no more than gaps in the columns of red cells.

The importance and the present state of the knowledge of the essential function of the capillaries, the exchange of substances between the blood and body tissues, are admirably reviewed by Landis.[6]

THE ARTERIOVENOUS ANASTOMOSES

Arteriovenous communications which are capable of short-circuiting the capillaries were first described anatomically by Sucquet in 1862. Heimberger[7] was able to observe such connections in the fingers of persons having very delicate skin. These channels are usually closed and open when there is a demand for the rapid movement of blood. Krogh[5] is of the opinion that the main function of these vessels is to supply enough blood to the projecting parts of warm-blooded animals to supply heat when the animals are exposed to low temperature.

In addition, Wright[8] has observed small anastomosing vessels which connect different segments of the capillary loop. They may connect the arterial limb with the venous or two portions of the venous loop. The blood may cease to flow through these connections while it still flows through the loop. Wright believes that these are probably residual vessels from the arciform capillaries of early infancy. They are few and are not to be confused with the arteriovenous shunt.

Grant and Bland[9] emphasize the importance of the arteriovenous anastomoses and the part they play in the vascular reactions of the extremities. The authors are in agreement with Krogh that the chief function of these structures in man and in animals is to maintain the temperature of exposed parts in which they occur.

Anastomoses are present in the fingers and are particularly numerous in the distal portions but do occur in the sole and palm, all locations in which the hyperemic reactions to cold are most marked.

However, from their limited distribution it seems unlikely that they can be more than a minor factor in the regulation of body temperature in man, who has other mechanisms more effective for the purpose.[9] In the rabbit's ear this function is important. But it is apparent that these anastomoses must be taken into consideration in dealing with the peripheral circulation in whatever areas they do occur because of their numbers as well as their activity.

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7. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren, Ztschr. f. d. ges. exper. Med. **56**:519, 1925.

8. Wright, I. S.: Intracapillary Anastomoses, J. Clin. Investigation **2**:835 (July) 1932.

9. Grant, R. T., and Bland, E. F.: Observations on Arteriovenous Anastomoses in the Human Skin and in Bird's Foot with Special Reference to the Reaction to Cold, Heart **15**:385 (July) 1931.

Popoff [10] has made careful anatomic and histologic studies of the arteriovenous anastomoses in man in normal and in pathologic conditions. The anastomoses are found almost exclusively over the ventral surfaces of the hands and feet and are constantly present in the region of the nail bed and in the tips of the fingers, the palmar surfaces of the first, second and third phalanges and the thenar and hypothenar eminences of the hand. Their distribution in the foot corresponds to that in the hand. In the skin they are located a little deeper than the web of subpapillary arteries and veins. They are uniform in appearance, with a narrow and irregular lumen. The layers which overlie the endothelium are indistinct but apparently consist of a muscular coat with inner longitudinal and outer circular layers. Numerous nonmedullated nerve fibrils lie in the collagenous outer zone. The collecting veins into which these vessels drain are characterized by a thin wall almost devoid of muscular cells. These veins surround the arteriovenous canals in the form of plexuses. The primary collecting veins open into the subpapillary veins.

The terminology employed by Popoff is distinct. The entire anastomotic unit is called the glomus. It consists of the afferent artery, the arteriovenous anastomosis (called the Sucquet-Hoyer canal), the neuroreticular and vascular structures around the canal, the outer collagenous tissue and the primary collecting veins. Capillaries are richly supplied to the collagenous area surrounding the canals. These apparently arise from preglomic arterioles given off from the afferent artery and finally enter into the limbs of the small plexus of veins surrounding the anastomosis, the primary collecting veins. Beyond the glomus the artery divides in the subpapillary layer into the arterioles and capillaries of the stratum capillare.

The beginning of the Sucquet-Hoyer canal is marked by the presence in the afferent artery of cushion-like endothelial muscular elevations, the function of which is to direct the blood flow into the Sucquet-Hoyer canals and preglomic arterioles.

The theory of function of the glomus, according to Popoff, is the regulation of heat locally as well as the regulation of body temperature as a whole. With exposure of the hand to cold the blood is diverted from the capillaries through the anastomoses into the collecting veins with a highly developed surface area, thus maintaining a constant local temperature. When the glomic system is fully opened as a result of the general reaction for the dispersion of heat, an enormous flow of blood may take place through the digits, allowing for the rapid loss of heat, which is limited by the very slow flow through the capillaries. The

10. Popoff, N. W.: The Digital Vascular System, with Reference to the State of the Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thrombo-Angiitis Obliterans and Supernumerary Digits in Man, Arch. Path. **18**:295 (Sept.) 1934.

glomus can also relieve the peripheral arterial system if the pressure within becomes very high, by shunting the blood across to the deep veins. In a like manner capillary stasis can be relieved. In man these anastomoses are under the control of vasomotor nerves.

The digital glomus is formed only after birth and in the aged undergoes atrophy. As the result of pathologic destruction a new canal can develop from one of the preglomic arterioles.

In cases of arteriosclerotic gangrene and diabetic gangrene two different processes present themselves. In the first there is hyaline degeneration of the afferent artery, while in cases of diabetic gangrene the Sucquet-Hoyer canal and the preglomic arterioles are involved primarily.

In cases of thrombo-angiitis obliterans there are no primary thrombotic or inflammatory reactions. A new idea as to the pathogenesis of the disease is presented in the discovery of many newly developed anastomoses between arteries and veins and between veins themselves. These anastomoses are pathologic and differ entirely from those of the normal glomus. They are purposeless and detrimental to the circulation.

THE NERVE SUPPLY OF THE BLOOD VESSELS

The essential nerve supply [11] to the blood vessels of the extremities is derived from that part of the autonomic nervous system which from its location in the long chain of ganglionated nerve cords extending vertically through the abdomen, thorax and neck is called the thoracolumbar or sympathetic portion. Preganglionic fibers arise from nuclei in the gray matter of the spinal cord, travel through the ventral roots and by way of the white rami enter the sympathetic system, where they turn either upward or downward and run for varying distances before terminating in synaptic relationship with the nerve cells of the sympathetic ganglions. From this point the postganglionic fiber begins, and it emerges from the sympathetic ganglion through the gray rami communicantes to the spinal nerves through which the postganglionic fibers then travel to supply the blood vessels, the secretory activity of the sweat glands and the pilomotor function of the hair follicles.

The cervical sympathetic trunk is composed almost exclusively of preganglionic efferent fibers derived through the white rami from the upper thoracic nerves and ascends to terminate in the cervical sympathetic ganglions. The lumbar and sacral portions of the trunk are composed in the major part of descending fibers from the white rami of the lower thoracic and upper lumbar spinal nerves.

It is important to note that the nerve supply to the arteries of the extremities is carried by the somatic nerves and segmentally distributed

11. Ranson, S. W.: The Anatomy of the Autonomic Nervous System with Special Reference to the Innervation of the Skeletal Muscles and Blood Vessels, Ann. Int. Med. **6**:1013 (Feb.) 1933.

to the blood vessels. The work of Ranson [11] and Kuntz [4] as well as the observations of many others is conclusive on this point. Ranson states that branches from the celiac ganglion and the plexuses which follow the aorta continue to the iliac vessels, where small plexuses are formed. Branches from these extend down the femoral arteries for a relatively short distance to terminate. They are relatively few in number and can be followed no farther. This is apparently the only exception. Beyond this point the vascular nerves are carried by the somatic nerves and are thereafter supplied to all the vessels, including the capillaries, in such a manner that the vascular distribution of nerve supply corresponds closely to the sensory distribution of nerves in the skin of both the upper and the lower extremities so that interruption of the sympathetic system by anesthetization of, for example, the median nerve produces peripheral loss of vascular tone in an area of the skin corresponding to the sensory distribution of that nerve in the hand.

That the sympathetic nerves to the blood vessels are vasoconstrictor has long been known, but to what extent the peripheral blood vessels are supplied by vasodilator nerves is uncertain.[4]

Lewis and Pickering [12] report experimental data which they believe indicate the existence of vasodilator as well as vasoconstrictor fibers in the sympathetic nerves to the extremities. They found that in normal persons vasodilatation could be observed in the hands when they were exposed to a room temperature of from 14 to 16 C. if the body was enclosed in a warm chamber. There would be a marked rise in the temperature of the fingers and hands when the body was warmed. In a patient with Raynaud's disease ulnar interruption of the sympathetic nerves by the injection of a local anesthetic failed to bring about vasodilatation in the area supplied at the environmental temperature of from 14 to 16 C. If, however, the same patient's body was placed in the warm chamber with the hands exposed to the same environmental temperature, complete vasodilatation took place in the hand except in the finger the nerve supply of which was blocked. Thus Lewis and Pickering concluded that simply inhibition of vasoconstriction cannot account for these variations and that the presence of vasodilator fibers in the sympathetic nerves of man must be admitted.

McDowell [13] states that the nerve supply to the capillaries has been repeatedly demonstrated, but that the full physiologic significance of this fact has taken many years to be appreciated. The vasoconstrictor

12. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to the Warming of the Body with Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

13. McDowell, R. J. S.: Nervous Control of the Blood Vessels, Physiol. Rev. **15**:98 (Jan.) 1935.

nerves affect both the arterioles and the capillaries as well as the larger vessels. It is also certain that veins are capable of constriction, although the mechanism by which this occurs is not discussed. It seems that the veins must have a connection with the nervous system.

The more than occasional failure to obtain permanent complete peripheral vasodilatation in man following sympathetic ganglionectomy and ramisectomy, particularly in the upper extremities, is usually explained by failure to interrupt all the sympathetic constrictor fibers because of anatomic difficulties and variations in the location and form of the ganglions.[14] In the lower extremities results seem to be more permanent in the majority of instances.

That the peripheral vessels are capable of maintaining a degree of tone after a certain interval independent of their nerve supply in animals has long been known. Whether or not this applies to man has been questioned.[4]

In a carefully studied case [15] in which there was complete peripheral vasodilatation with all the concomitant signs of removal of the superior cervical and second thoracic sympathetic ganglions, the tone of the peripheral vessels returned to the normal preoperative level within twenty-one days. A digital plethysmograph was employed as a direct measure of the circulation. The temperature of the skin remained elevated, the function of the sweat glands remained inhibited, and Horner's syndrome persisted. It was possible to induce vasodilatation in the digits by immersion of the hand in hot water to the same degree as that of the normal side. Following the induction of artificial fever there was the usual vasodilatation in the normal digits; on the side on which sympathectomy has been performed there was no vasodilator response. This would also indicate that the denervation was complete, since no peripheral response to the release of central tone was possible, as it occurred in the normal side. This result is in keeping with the results of experiments on animals in which preoperative tone is reestablished in from ten to fourteen days after sympathectomy, and it is not logical to assume that the control of vascular tone is much different in man from that in animals. Also, the increased temperature of the skin, usually considered to be an index of increased flow of blood, to the part, following sympathetic ganglionectomy may be largely due to a loss of part of the heat-regulating mechanism.

14. Adson, A. W.: The Results of Sympathectomy in the Treatment of Peripheral Vascular Diseases, Hirschsprung's Disease and Cord Bladder, Ann. Int. Med. **6**:1044 (Feb.) 1933.

15. Johnson, C. A.; Scupham, G. W., and Gilbert, N. C.: Studies in Peripheral Vascular Phenomena: II. Observations on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, Surg., Gynec. & Obst. **55**:737 (Dec.) 1932.

Coller and Maddock [16] comment on the fact that interruption of the sympathetic pathway results in the exclusion of the extremity in which interruption was effected from participation in the regulation of the heat of the body by interruption of the vasoconstrictor effect by which the dispersion of heat is prevented. It is the loss of this function which they believe results in an increased flow of blood to the extremity.

In contrast to this, Adson [14] cites the observations of Waggoner on the vessels of the fundus after cervicothoracoganglionectomy and resection of the trunk in Raynaud's disease. Both the arteries and the veins dilate from one and one-third to one and one-half times their preoperative diameter, and the dilatation is permanent. He states that the increased flow of blood as indicated by the increased elimination of heat continues and does not recede to the preoperative level. The capillaries are seen to be smaller in diameter than those noted in the cyanotic phase of Raynaud's disease, but the stream of corpuscles is seen to flow much faster.

McDowell,[13] in an excellent review of the subject, states that even after all the nerves to a part are cut the peripheral vessels in animals in time recover their normal caliber. In regard to the vessels responsible for the recovery, he cites the work of Herrick, Essex and Baldes to show that the large vessels are not concerned with the recovery of tone. Their observations thirty-four months after sympathectomy revealed an increased flow of blood in the femoral artery of the side on which the operation was performed. McDowell believes that the capillaries themselves seem to be the most likely location for the opposing effect, which he thinks is probably the result of the action of chemical agents normally present in the circulating blood. This is a direct effect on vascular tone, and the vessels are more sensitive to chemical influences soon after denervation. When the nerves fully degenerate the reaction disappears.

McDowell also states that it is difficult to imagine that there is a fundamental difference between man and animals in regard to sympathetic denervation, although clinical evidence in many instances seems to point in this direction.

In regard to the chemical and hormonal effects on the blood vessels after sympathectomy in man, Freeman, Smithwick and White [17] found

16. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, Ann. Surg. **100**:983 (Nov.) 1934.

17. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Reactions of the Blood Vessels of the Human Extremity Sensitized by Sympathectomy to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia, Am. J. Physiol. **107**:529 (March) 1934. Smithwick, R. H.; Freeman, N. E., and White, J. C.: The Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause for Failure of Operations for Raynaud's Disease, Arch. Surg. **29**:759 (Nov.) 1934.

that the blood vessels of the extremities become more sensitive to epinephrine after sympathectomy. The increased sensitivity develops from six to eight days after paralysis and does not occur in acutely denervated areas following immediately after nerve block by a local anesthetic.

The intravenous infusion of a 1:250,000 solution of epinephrine, which causes little change in the normal side, is sufficient to cause a lowering of surface temperature as much as 15 F. on the denervated side. The same thing happens when the adrenal glands are stimulated by hypoglycemia caused by insulin. Identical vasospastic phenomena which occur in sympathectomized cats and in rabbits with hypoglycemia caused by insulin can be abolished by adrenal denervation.

THE FUNCTIONS OF VASOCONSTRICTION AND VASODILATATION

It is by constriction that the normal tone of the peripheral vessels is maintained. The degree is constantly fluctuating in response to environmental changes in temperature, internal production of heat and emotional reactions. Perhaps the most constant effect is that of response to the requirements of the body for the maintainance or dispersal of heat. Lewis and Pickering [12] have shown that when a person lightly clad is exposed to an environmental temperature of from 16 to 18 C. constriction of the vessels of the skin of the hands and feet is in high degree. An increase in the environmental temperature to a higher level results in release with an increased surface temperature. The vasodilatation which occurs is accomplished in part by a direct effect on the vessels of the skin and by the effect of the warmed blood on the central temperature-regulating mechanism which results in vasodilatation by action through the central nervous system.

The authors found that if the body was warmed while the hands were exposed to a temperature of from 14 to 16 C. vasodilatation took place in the hands. The finger-tips warmed first, then the base and finally the hand. Cooling occurred in the same order. The response of dilatation occurs earlier in the fingers than in the toes. Exceptionally vasodilatation may fail to occur in the toes. This delayed response is interpreted not as a difference in vascular tone but as a difference in the intensity of the vasomotor relaxation in the upper and lower extremities. With warming of the body to a higher degree or increase in the environmental temperature relaxation could occur.

Normal vascular reaction to cold has been studied by Sir Thomas Lewis.[18] This reaction is expressed locally by vasodilatation preceded by constriction when one finger is immersed in cold water for a period of from five to ten minutes. The vasodilatation continues during

18. Lewis, T.: Observations upon the Reaction of the Vessels of the Human Skin to Cold, Heart **15**:177, 1931.

immersion, often giving rise to a phasic rise and fall of temperature. After the finger is removed the temperature rises well above that of the uncooled digits. The temperature rises gradually and then falls slowly. The lower the temperature the more marked is the reaction. This reaction can be elicited from the fingers, toes, ears and parts of the face. It is considered that this reaction is the result of an axon reflex of a sensory nerve which is activated by the release of the so-called H substance of the skin. The function of this mechanism is the protection of exposed parts from injury by exposure to cold.

The same type of reaction occurs as the result of exposure outdoors provided the body is kept warm and only the hands are exposed. At first the temperature of the finger falls to near that of the environmental temperature; this is followed by a rise after an interval of about one hour to a level of from 4 to 13 C. above the minimum. The more quickly the fall occurs, the more rapid is the reactive vasodilatation. The fingers are painful while the temperature is low and rapidly become comfortable as soon as the reaction sets in.

This reaction fails to occur if the body is not kept warm. If larger surfaces of the body are cooled, then general vasomotor tone is increased and local reactive hyperemia cannot occur. If the finger is immersed in ice-water while the opposite arm is likewise immersed in water at a temperature of from 15 to 25 C. at a room temperature of from 19 to 21 C., the reaction seldom occurs. If the temperature of the bath of the opposite arm is increased to 30 C., the reactive hyperemia is invariable.

When the entire body or larger portions of it are exposed to cold or protection is inadequate, the blood vessels of the skin become constricted. The cooling of one hand when the other is immersed in ice water has long been known but has been usually considered to be a vascular reflex from the skin by the stimulus of cold. Pickering[19] states that the whole surface of the skin reacts in the same way. He says: "Vasoconstriction arising reflexly from a cold stimulus applied to the skin seems to be securely established by the work of Franck," but he advances experimental proof that this is not the sole mechanism, although his observations do confirm those of Franck. The mechanism is of a dual nature. In addition to the direct stimulation which gives rise reflexly to cutaneous vasoconstriction, which he has found to be of short duration and which is an immediate response, the essential mechanism is the result of the effect of the cooled blood, flowing from the cold part, on the central temperature-regulating mechanism, through which general vasoconstriction occurs.

19. Pickering, G. W.: Vasomotor Regulation of Heat Loss from the Human Skin in Relation to External Temperature, Heart **16**:115, 1932.

Pickering has further shown that the effect of the application of heat brings about essentially the same type of response. General vasodilatation follows an increase in the enviromental temperature, and likewise the exposure of one member to increased temperature by immersion in warm water results in general vasodilatation, but the mechanism by which this occurs is single. There has been no proof advanced, according to Pickering,[19] that a central nervous reflex plays any part in the general vasodilatation which follows, but all the experimental evidence which he has accumulated indicates that the phenomenon is a direct effect on the temperature-regulating mechanism (not the temperature center) by the effect of the warmed blood flowing from the warmed part, which results in a general vasomotor release of tone with general vasodilatation in the attempt to increase the elimination of heat from the surface of the body.

The local effect of heat on the blood vessels is in part a direct action on the walls of the vessels, which respond by dilatation, and in part the result of the increased amount of warmed blood from the heated extremity on the central temperature-regulating mechanism. It seems probable that the local effect is the direct release of vasoconstrictor tone which exceeds the normal constrictor tone exerted by the vasomotor system. In addition to the effect on the larger vessels, those of the skin are effected directly by the release of the familiar H substance, especially following the injury which is produced by immersion in water at higher temperatures.

After permanent interruption of the sympathetic pathway by ganglionectomy it has been possible to demonstrate dilatation of the digital arteries after immersion of the hand in hot water by observation of the increase in pulsations of these vessels, which could then be abolished by cold.[20] The same reactions have been observed by means of plethysmographic measurements of circulation following cervicodorsal sympathetic ganglionectomy and ramisectomy. Essentially the same degree of vasodilatation could be induced in the denervated hand as in the normal hand by direct immersion in hot water. Induction of fever by the injection of typhoid vaccine intravenously resulted in no change in the vessels of the denervated finger, while in the normal finger, the usual vasodilatation took place.[15]

Maddock and Coller,[21] in a more recent publication, call attention to the important part played by the extremities in the control of body temperature. The surface of the skin dissipates 76 per cent of the total

20. Lewis, T., and Landis, E. M.: Some Physiological Effects on Sympathetic Ganglionectomy in the Human Being and Its Effect in Raynaud's Malady, Heart **15**:151, 1930.

21. Maddock, W. G., and Coller, F. A.: The Rôle of Extremities in the Dissipation of Heat, Am. J. Physiol. **106**:589 (Dec.) 1933.

heat produced by conduction, convection and radiation. Twenty-four per cent is eliminated by the vaporization of water from the surface and by the lungs. This is at comfortable environmental temperatures. With an increase in the environmental temperature or with hard labor, sufficient heat cannot be eliminated in this way, and vaporization increases so that it may account for almost all the heat lost.

Maddock and Coller consider that the temperature of the skin at any one point is a resultant of the heat brought to it largely by its blood supply and the heat lost from its surface. There is a gradient from the deep tissues of the extremity to its surface. When the skin is cool there is a depth of from 3 to 5 cm. where the temperature is less than that of the blood. The gradient is diminished by exposure to heat and increased by cold.

With these considerations in mind, under carefully controlled conditions Maddock and Coller were able to show a marked increase in the surface temperature of the extremities above that of the rest of the body, demonstrating a much greater degree of peripheral vasodilatation here than on the head or trunk. The same result was apparent with changes in the internal production of heat when the temperature and humidity were kept constant. Under these conditions the temperature of the toe showed a straight line relationship to the basal production of heat per unit of surface area.

The extremities show great variations in vasoconstrictor tone because they are normally called on to take a major part in the conservation or elimination of heat, a part they are particularly adapted for as they contain no vital organ. They supply 65 per cent of the total body surface and are thrust out into their environment in such a manner as to make the dissipation of heat effective.

An interesting comment is made in regard to the normal tone of the vessels of the extremities resulting from the heat-conservation mechanism being confused with angiospasm.

DIAGNOSTIC METHODS

In many cases a diagnosis of peripheral vascular disease can be made without the use of special equipment. In some cases all the information obtainable fails to allow a conclusive decision. This is particularly true in the differentiation of various types of circulatory impairment. Reid [22] comments on the importance of early diagnosis of vascular disease in the extremities, because by relatively simple therapeutic measures applied at an early stage many persons may be spared the consequences of gangrene. The means for estimating the circu-

22. Reid, M. R.: Diagnosis and Treatment of Peripheral Vascular Diseases, Am. J. Surg. **24**:11 (April) 1934.

latory efficiency are as accurate as those for the heart and kidneys and should be included in all routine and general physical examinations.[22]

Most of the methods of examination by inspection and palpation have been described in detail in earlier publications by Buerger,[23] Silbert,[24] Brown[25] and many others. Particularly those subject to errors of interpretation and the more recent methods are considered here.

The importance of careful general examination has been emphasized many times.[26] This is particularly true in regard to consideration of the cardiovascular system. Impairment of cardiac function, particularly with disorders of mechanism, may be responsible for the rapid exaggeration of symptoms referable to structural arterial diseases in the extremities. Metabolic and infectious diseases are frequently the cause of circulatory impairment or may simulate impairment when circulation is adequate.

Disease of the central or peripheral nervous system is capable of simulating vascular disease and is often a common cause of peripheral vasospastic phenomena. The Raynaud syndrome is not uncommon as a manifestation of other diseases, including scleroderma and rheumatoid arthritis, while acrocyanosis is nearly always secondary. While vascular disorders have frequently been mistaken for static orthopedic diseases, the converse is also true.

Obliterating arteriosclerotic disease is frequently part of general arteriosclerosis, and cerebral, cardiac and other manifestations may be simultaneous. While the phenomena of hypertension are usually visceral, there are occasionally peripheral accidents. Thrombo-angiitis obliterans is essentially a peripheral vascular disease, but visceral vascular disease has been reported with increasing frequency, while the opposite is true of periarteritis nodosa. Severe anemia, by pallor and even by intermittent claudication,[27] may simulate obstructive disease, while in polycythemia both thrombosis and vasodilator phenomena are common.

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23. Buerger, Leo: The Circulatory Disturbances of the Extremities including Gangrene: Vasomotor and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924.

24. Silbert, Samuel: Studies in Thrombo-Angiitis Obliterans (Buerger): II. The Effectiveness of Therapeutic Procedures, J. A. M. A. **89**:964 (Sept. 17) 1927.

25. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

26. (*a*) de Takáts, Géza, and Mackenzie, W. D.: Diagnosis and Treatment of the Circulatory Disturbances of the Extremities, Surg., Gynec. & Obst. **58**:655 (March) 1934. (*b*) Weiss, Soma: Circulatory Disturbances of the Extremities: Medical Aspects, New England J. Med. **209**:267 (Aug. 10) 1933.

27. (*a*) Pickering, G. W.: On the Clinical Recognition of Structural Disease of the Peripheral Blood Vessels, Brit. M. J. **2**:1106 (Dec. 16) 1933. (*b*) Lewis, T.; Pickering, G. W., and Rothschild, Paul: Observations upon Muscular Pain in Intermittent Claudication, Heart **15**:359, 1931.

Thus it becomes increasingly evident that while essential progress has been made in the study of peripheral vascular disease, its consideration in relation to visceral disease should be appreciated. The difference in environmental relationship between the blood vessels of the extremities and those of the viscera as well as a difference in their functions renders them more susceptible to the development of both functional and organic disease.

Abnormalities of Appearance.—In a discussion of the clinical recognition of structural diseases of the blood vessels of the extremities, Pickering [27a] summarizes the abnormalities of appearance. These are, essentially, gangrene, which is the result of prolonged interruption of blood flow, and indolent ulceration, which follows impairment of the blood supply, spasmodic or organic, often associated with chronic infection. The abnormalities of color may be either change in normal depth or change in tint. They are varied, subject to errors of interpretation and yet important.

In the absence of severe anemia, local pallor indicates that the superficial vessels are empty. It usually occurs when blood is massaged out of a part and inflow is impaired by organic or spasmodic constriction of the vessels. Conspicuous pallor when a limb is maintained above the level of the heart strongly suggests structural impairment, because blood fails to enter it from the arterial side while it drains out into the venous circulation. If rapid cyanosis occurs when the limb is suddenly changed to a dependent position, the significance is increased. Persistent pallor may occur when the inflow of blood is limited to an extreme degree or the superficial vessels are constricted, as in Raynaud's disease during the pallid stage of the paroxysm. When the superficial vessels are not constricted, the color is dependent on backflow into the capillaries of the veins. Pallid skin is always cold if the color is dependent on impaired arterial inflow.

Increased depth of color, rubor, is due to dilatation of the capillaries and small vessels of the skin as the result of local injury by impaired blood supply, continued cold, low grade or chronic inflammation, ultraviolet irradiation or mechanical injury. Lewis [28] points out that redness of the skin does not indicate of itself an increased blood supply, because mere dilatation of the capillaries at the surface, even with considerable impairment of inflow, may result in redness. In this case it is associated with decreased skin temperature. Redness with normal or increased surface temperature is compatible with normal or increased circulation.

Local cyanosis is due to local slowing of the blood stream relative to the oxygen requirements of the skin. In a cold skin cyanosis may

28. Lewis, T.: Clinical Observation and Experiments Relating to Burning Pain in the Extremities and So-Called Erythromelalgia in Particular, Clin. Sc. **1**:175 (Dec.) 1933.

occur as a result of spasmodic constriction of arterioles yet capable of dilating. If the limb is warmed the vessels may be assumed to be dilated, and cyanosis here is strong presumptive evidence of structural disease above.

Postural changes in color are common in persons with organic disease of the arteries. Deepening of cyanosis of the skin when a limb is dependent is commonly due to stasis in the toneless superficial vessels with filling consequent on the static increase in venous pressure. In the event of rubor with dependence the change may be merely due to dilatation of the vessels of the skin consequent on local injury, but with cyanosis it is usually due to some impairment of circulation in addition. Marked variations in tint may be present between marked rubor and extreme cyanosis.

In appreciation of the value of observation of color and to establish an objective means of recording such variations, the color chart of Lewis [28] is applicable. However, extreme care must be exercised in the interpretation applied to variations in color. Local cutaneous injury or inflammation, impaired arterial inflow and obstructed venous outflow must all be considered. The rate of return of color produced by blanching of the skin by pressure of the finger is not reliable as a test of efficiency of the circulation.

Palpation of the Vessels.—The local condition of blood vessels as determined by inspection and palpation is an important and widely used criterion of the condition of the circulation. Arterial pulsations determined by palpation with the finger are open to certain errors of interpretation. It is generally assumed that when pulsation is present in the dorsalis pedis and posterior tibial arteries the arterial circulation is intact. Pickering [27a] points out that pulsation may be retained in the larger vessels when smaller distal vessels are occluded. Also, circulation may be nearly normal with the absence of pulsation as in coarctation of the aorta or impaired cardiac function. In extreme senile arteriosclerosis pulsations may be extremely weak or absent owing to sclerosis of the wall of the vessel, yet with entirely adequate circulation. Pickering [27a] also emphasizes the importance of temperature. In a very cold extremity pulsations may be very feeble. He states: "The failure of pulsation in an artery of a limb when body and limb are warm is the most certain sign we possess of structural disease of that vessel."

The frequency of anatomic variations from the normal has been discussed by Reich,[29] who states that all writers have referred to the pulses of the foot as a cardinal criterion of peripheral circulatory efficiency. Buerger thought that absence of the pulse occurs in only

29. Reich, R. S.: The Pulses of the Foot, Ann. Surg. **99**:613 (April) 1934.

0.5 per cent of normal persons and therefore is a finding of paramount importance in persons with peripheral vascular disease.

In observations on 500 normal healthy persons the dorsalis pedis artery was absent in 4 per cent and the posterior tibial artery in 5 per cent, while in another 8 per cent the dorsalis pedis artery was found in other than its usual position. It is evident, then, that the absence of these pulses cannot be interpreted as being due to disease without other confirmatory evidence.

In addition, extravascular factors diminish the ease with which these pulses can be felt. Edema, adiposity, tendons and ligaments interfere.

Reich says that variations are common because these vessels are of relatively recent phylogenetic origin. In primates other than man the popliteal artery ends in vessels in the muscle while the foot is supplied by a direct continuation of the femoral artery, the saphenous artery, which is absent in man. In man alone of all the primates is found the complete pattern of the new connections between the popliteal artery and its distribution on the dorsum and sole of the foot.

Visible capillary pulsations after warming an extremity by immersion in hot water are good evidence that circulation to the exposed part is intact.[27] Absence does not invariably indicate occlusion. Veins likewise share in the vascular relaxation caused by local heat, and superficial venous plexuses can be demonstrated by immersion in water at from 35 to 40 C., especially with the part dependent, or by obstruction of the veins by a pressure of from 60 to 70 mm. of mercury.

In the upper extremity the vessels show less variation, although the ulnar artery is less readily palpable. The presence of pulsation in these vessels likewise does not exclude organic disease because of the extensive blood supply to the hand and fingers. Pulsation of the digital arteries can usually be felt in normal persons after the immersion of the hand in hot water (40 C.), but again, the absence of pulsation without other corroborative evidence does not always indicate occlusion.[27] Allen's test is reliable, particularly when there is a striking difference in the reactions in the two hands. It is a test for the patency of the circulation of the radial and ulnar arteries beyond the wrist.

Ischemia.—The appearance of intermittent claudication in the absence of severe anemia may be taken as an indication that structural disease of the vessels is present.[27] In order to avoid possible errors in interpretation, Lewis, Pickering and Rothschild [27b] used an exercise test based on the following observation: The circulation of the leg of a healthy person is interrupted, and the ankle joint is repeatedly and fully extended against resistance at the rate of one complete movement a second. Pain appears in the muscles of the calf if the ankle is flexed; against extension pain appears in the anterior tibial muscles. The pain

appears in from twenty to thirty seconds and disappears in five seconds or less after circulation is released. If a patient with diseased vessels works his leg in the same way without circulatory arrest, then the time taken for the pain to appear, become unbearable and disappear after exercise provides a guide for the adequacy of muscular blood supply. As a basis for comparison, the time taken for the occurrence of these phenomena when the circulation is arrested can be estimated if a period of more than fifteen minutes is allowed to elapse between tests.

Samuels [30] has described a test for plantar ischemia which is of considerable value in determining inadequacy of arterial inflow to the foot. With the patient recumbent and the legs in the vertical position the feet are flexed and extended at the ankle. In addition to pain or fatigue, conspicuous pallor of the plantar surfaces occurs if the arterial circulation is inadequate. These findings are particularly important if they occur unilaterally.

Reactive Hyperemia.—The test for reactive hyperemia, if properly performed, is considered by Pickering [27a] to be as delicate as any single test yet devised and requires no apparatus but a sphygmomanometer. Two precautions are necessary. The vessels must be dilated to the maximum, which can be assured by having the body quite warm and the limbs to be tested warm enough to maintain maximum dilatation of the cutaneous vessels. The vessels of the skin must be emptied of blood before the circulation is arrested. In performing the test the limbs can be warmed by the application of external heat or immersion in water at from 35 to 40 C. They are lifted out of the water and elevated with the patient recumbent to empty the vessels. Circulation is then arrested by the application of a sphygmomanometer cuff above the level of systolic blood pressure for the limb. The limb is then lowered and kept warm. After four and one-half minutes it is laid horizontal in good light. One-half minute later the circulation is released. A flush appears in the extremity and its course is observed. When the vessels are patent, as in normal persons or in persons with uncomplicated Raynaud's disease or acrocyanosis, the flush reaches the digits in less than five seconds. It is bright and reaches maximum intensity in less than fifteen seconds and fades quickly. In structural disease the flush spreads slowly, is patchy or mottled and is considerably delayed to the tips of the digits, even to a minute or more. The flush is somewhat cyanotic in tint and lasts longer. All patients known to have structural disease have, in the experience of Pickering, shown an abnormal reaction indicating obstruction to the inflow of arterial blood to the vessels of the skin.

30. Samuels, S. S.: The Early Diagnosis of Thrombo-Angiitis Obliterans: A New Diagnostic Sign, J. A. M. A. **92**:1571 (May 11) 1929.

Surface Temperature.—It has been said that this is perhaps the most important indication for the determination of the adequacy of blood flow through a limb.[27a] Certainly it is the most widely used and relied on of the objective means of measurement. The temperature of the skin at any one point is the resultant of the heat brought to it, largely by its blood supply, and the heat lost from its surface.[21] It is evident that there are wide fluctuations in health, and because of this as well as because of the effect of environmental conditions, observations must be carefully controlled. The blood flow to the skin is of great importance in the maintenance of body temperature. The effect of exposure to cold is, first, a direct action on the superficial arterioles resulting in their constriction and, second, generalized vasoconstriction of the vessels of the skin evoked in part reflexly by stimulation of the skin by cold and in part by action of the cooled blood on the central temperature center. When prolonged or extremely cold short exposures occur, reactive vasodilatation follows. It is assumed that under these conditions the arteriovenous anastomoses also open.[5] When the air is cool and the entire body is cooled the peripheral vessels are constricted and the skin temperature is low. When this mechanism is no longer adequate to control the temperature of the body with the patient at rest or with minimal internal production of heat, shivering occurs.[21] The skin is further cooled by evaporation, which is dependent on the amount of moisture on the surface and its rate of evaporation, which in turn is dependent on environmental temperature, relative humidity and air currents.

Increased environmental temperature results in vasodilatation and increased surface temperature. In addition to these environmental factors, there are those dependent on the individual patient, his body temperature, rate of metabolism and emotional reaction, which result in constantly varying vasomotor changes. Yet when these factors are controlled with reasonable care, the skin temperature is a sufficiently reliable guide as to the efficiency of the circulation for practical clinical objective use. It has been shown, however, that observations on skin temperature after sympathectomy are no longer a reliable measure of the circulation because, in part at least, of the abolition of the function of the sweat glands and failure of loss of heat by evaporation.[15]

It is apparent, then, that coldness of the extremities alone does not suffice for the diagnosis of arterial disease or spasm. Inequality of temperature between two symmetrical extremities is of the utmost importance if they are similarly treated and exposed for the same length of time to the environment. Unilateral coldness almost always indicates structural disease of the vessels. Rarely, the reverse is true because of the opening of collaterals of the skin and subcutaneous tissues.[19]

The temperature gradient is also important. A sudden decrease in temperature from the proximal to the distal portion of an extremity is evidence of impairment of circulation.[31]

Readings of surface temperature are particularly important in observations after the removal of vasoconstrictor tone, which will be considered later.

A rough idea of differences in the surface temperature can be obtained by simple palpation in properly controlled surroundings. Differences of 1 C. can be appreciated, and when it is considered that in cases of obstructive disease there may be variations of 3 degrees or more, such a measure may be of considerable diagnostic value in conjunction with other simple tests. A mercury thermometer of special type has been used by some observers,[26a] but others consider it unreliable. The most widely used method is that of some form of thermoelectric couple by which accurate readings are quickly obtained.

Calorimetric determinations have been largely supplanted by measurement of skin temperature under controlled conditions.

Oscillometry.—By means of the Pachon oscillometer or instruments of similar type information as to the state of the larger and deeper arteries of the extremities may be obtained.[32] Friedlander [33] has noted that the maximum oscillometric phase is variable in many conditions and even in the same person. The form of the oscillogram is important, and Friedlander has noted four distinct types, the normal type and those of arteriosclerosis, hypertension and medial sclerosis. Mixed forms appear in some persons. Oscillograms must be interpreted on the basis of the factors which maintain blood pressure, the force of the cardiac contraction transmitted to the point of observation, the condition of the walls of the blood vessels and the degree of peripheral resistance as well as other uncertain factors, possibly the volume and viscosity of the blood.

Simpson [34] has shown the importance of the use of a standard technic. Variations in the application of the cuff often lead to error.[31] The shape and height of the oscillogram determined at different levels of the same extremity and compared with readings at symmetrical levels

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31. (*a*) Brown, G. E.: Thrombo-Angiitis Obliterans, Surg., Gynec. & Obst. **58**:297 (Feb. 15) 1934. (*b*) de Takáts and Mackenzie.[26a]

32 Samuels, S. S.: The Value of Oscillometry in the Study of Circulatory Disturbances of the Extremities, J. A. M. A. **88**:1780 (June 4) 1927. de Takáts and Mackenzie.[26a]

33. Friedlander, A. I.: Studies in Oscillometry, Am. Heart J. **9**:212 (Dec.) 1933; Recognition of Types of Arteriosclerosis by Oscillometry, J. A. M. A. **104**:297 (Jan. 26) 1935.

34. Simpson, S. L.: Instrumental Methods in the Study of Peripheral Vascular Diseases, Am. Heart J. **6**:309, 1931.

of the other extremity give a fairly accurate idea of the arterial inflow through the larger arteries. Readings taken above and below arterial occlusions demonstrate the site of the lesion.[26a] The test does not, however, determine the extent of the collateral circulation. Used in conjunction with other tests, it is of particular value in organic arterial disease.

Comparison with the reaction to histamine made by Kramer [35] led him to believe that these tests are nearly parallel in efficiency. It may indicate an efficient circulation in a limb with definitely diseased arteries if the collateral circulation is effective. De Takáts says that the histamine test is capable of determining the extent of collateral circulation, which he thinks is not possible with the oscillometer.

Samuels [32] comments on the fact that in some cases of thromboangiitis obliterans in which the readings are zero over a considerable extent of the leg, there is no evidence of impairment of integrity of the tissues. He assumes that in such cases the arterial flow consists of seepage or ooze through canalized vessels or collateral circulation rather than a pulsatile current.

In spite of these and other shortcomings, the oscillometer is capable of giving information concerning the vessels of an extremity as a group which is not obtainable in any other way except perhaps by arteriography.

Plethysmographs.—Johnson [36] has introduced a recording plethysmograph of an exceedingly sensitive type which is easily used, compact and simple to operate. It is capable of measuring and supplying a permanent record of the changes of volume in a digit which result from each ventricular contraction with accuracy to 0.002 cc. The instrument consists of a glass cup, which is applied to any digit, with an air conduction system which actuates a bubble of alcohol in a graduated 1 cc. pipet. The movements of the bubble are recorded on a moving strip of electrocardiograph paper together with the volumetric markings on the pipet, which furnish the means of measuring the changes of volume in the digit against the oscillations of the bubble of alcohol. By this method inertia and friction have been reduced to a minimum.

The observations can be employed in the same ways that observations on skin temperature are used both for the determination of the existence of structural disease and angiospastic conditions and for their differentiation with the release of vasoconstrictor tone.[15] The sensitivity of the device is demonstrated by the fact that disturbances in cardiac

35. Kramer, D. W.: Evaluation of Various Methods of Investigating the Circulation of the Lower Extremities, Am. J. M. Sc. **185**:402 (March) 1933.

36. Johnson, C. A.: Studies of Peripheral Vascular Phenomena: I. A New Device for the Study of Peripheral Vascular Phenomena in Health and Disease, Surg., Gynec. & Obst. **55**:731 (Dec.) 1932.

mechanism are shown by the variation in form and time of the pulse wave. After the induction of vasodilatation by the local application of heat there is a remarkably constant form to the pulse wave, which is often individual for the same digit in structural disease. The instrument is capable of the demonstration of defects into the digit but gives no indication of the location of the point of stenosis. It does indicate to some extent the presence of collateral circulation.

Observations on skin temperature often closely parallel the findings but show a considerable lag with increases in vasodilatation. The instrument is not subject to all the limitations of observations on skin temperature, particularly in that the cooling of evaporation, air currents and minor changes in environmental temperature have no direct effect. After sympathectomy, when the skin temperature is elevated, the plethysmograph may show very small pulse waves due to increased vascular tone. This occurs late, from two to three weeks afterward, and not after acute interruption of the vasomotor pathway. It is subject to the same emotional and general vasomotor reactions and has the additional advantage that observations may be made on an extremity immediately after exposure to heat or cold by immersion. This should make this method particularly valuable in the diagnosis of disease in the smaller digital arteries.

Reaction to Histamine.—Following the work of Lewis,[37] Starr[38] and de Takáts[39] utilized the cutaneous reaction to histamine as an indication of circulatory efficiency. The latter used an intracutaneous method with the injection of 0.1 cc. of a 1 : 1,000 solution of histamine with observations on the resulting flare. De Takáts emphasizes the importance of having the extremity in the horizontal position, because the level of the part has a determining effect on the reaction. He found that the results of this test follow the observations on skin temperature fairly closely and can be correlated with the oscillometric findings but give a much better indication of the efficiency of the collateral circulation, which the oscillometer fails to reveal. The intensity of the response to histamine followed the temperature gradient of the extremity when there was organic impairment of the arterial blood flow. With improvement of the circulation as a result of successful treatment, the peripheral extent of the histamine test was reflected in the improvement. The test

37. Lewis, Thomas: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

38. Starr, Isaac, Jr.: Change in the Reaction of the Skin to Histamine, J. A. M. A. **90**:2092 (June 30) 1928.

39. de Takáts, Géza: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**:769 (Nov.) 1931.

was accurate in all cases in which there was evident structural arterial impairment except those in which collateral circulation was adequate and in which circulatory impairment was suggested by the oscillometric readings. De Takáts found that the reaction was modified by vasoconstriction of the small blood vessels of the skin. When vasoconstriction was induced by immersion of the part in cold water there was a failure of normal response. The same reaction occurred in cases of vasospastic disorders, such as Raynaud's disease, and, as Lewis [37] previously showed, when the circulation was occluded by application of a cuff for the testing of blood pressure inflated above systolic pressure. The flare appeared, however, when the obstruction was released and blood was admitted to the extremity so that the dilated vessels could be filled. In conjunction with other tests it has proved to be of confirmatory importance in establishing the location of the optimum level of amputation. In short, the test is an indication of the available flow of blood into the vessels of the skin and the state of contraction of these vessels. It is a simple clinical test which may be used to determine the presence of adequacy of the cutaneous collateral circulation and together with the other usual tests affords an estimate of the efficiency of the circulation of the extremities.

Kramer [38] found essentially the same relationship between the histamine and the oscillometric test for circulatory efficiency. He decided that a prompt normal reaction indicated a satisfactory circulation, which might be adequate even when some of the deeper vessels were apparently occluded. The wheal and flare should appear within five minutes, and he considers that a delay is evidence of impairment of circulation.

Perlow [40] advises a test using a 1:2,000 solution of histamine in a 0.5 per cent solution of procaine hydrochloride. The reaction is said to be essentially the same as that of others and when used intradermally is painless.

Release of Vascular Tone.—Measurement of vascular tone has been widely used both for the determination of structural disease and for its differentiation from vasospastic disorders as well as for investigation of the degree of vasospasm imposed by, or occurring in conjunction with, organic obstruction. In addition, it is the principal method by which the success of sympathetic ganglionectomy might be indicated. Measurements of skin temperature are used in general for the measurement of the degree of vasodilatation secured, but plethysmographic methods are at least as accurate.[41]

40. Perlow, S.: A Painless Histamine Test: An Experimental Study, Ann. Int. Med. **7**:561 (Nov.) 1933.

41. Scupham, G. W., and Johnson, C. A.: Peripheral Vascular Phenomena: III. The Peripheral Pulse Volume in Occlusive Arterial Diseases, Arch. Int. Med. **52**:877 (Dec.) 1933.

Peripheral vasodilatation is generally produced by one of three methods in the clinical study of vascular diseases: (1) increased internal production of heat; (2) increased environmental temperature applied locally or generally, and (3) temporary interruption of the vasoconstrictor pathway through the sympathetic nervous system.

Brown [42] introduced and has used the method of artificial induction of fever by the intravenous injection of typhoid vaccine to secure marked peripheral vasodilatation. The rise in temperature of the distal portions of the extremity in the absence of organic obstruction to the flow of blood increases much more than the increase of body temperature if the initial temperature is sufficiently low. This he has expressed as the vasomotor index, which is calculated by subtracting the increase in oral temperature from the increase in peripheral temperature with the result divided by the increase in oral temperature. Normal values are from 2 to 10. If a temperature of at least 29 C. (84.2 F.) is reached in the skin of the affected digits after fever is induced, satisfactory ability for vasodilatation is assumed to exist. Conversely, if the rise is small, high grade obstruction is present with little or no capacity for vasodilat tion. This method is not applicable to ambulatory patients and is contraindicated for those with arteriosclerotic disease, the aged and those debilitated from other causes.

Landis and Gibbon [43] were able to secure efficient vasodilatation in the extremities by immersion of the two opposite members in water at a temperature of from 40 to 45 C. for a period of about thirty minutes. Within certain limits they found this method to be sufficiently effective for the usual clinical diagnostic purposes. When the hands were immersed the temperature of the toes rose to 31.5 C. or more in normal persons, which Scott and Morton [44] regard as the minimum normal rise following general and spinal anesthesia. In the event of organic structural impairment of circulation there was a much more limited rise in the affected extremities comparable to the grade of impairment. In comparison with other methods for the inhibition of vasoconstrictor tone, it was found that in most instances of structural insufficiency this method was equally satisfactory in result and much easier to carry out. In a few cases Landis and Gibson were able to secure evidence of dilatation of the peripheral vessels by artificial fever or nerve block when vasoconstrictor tone could not be completely released

42. Brown, Allen and Mahorner.[25] Brown.[31a]

43. Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities with Reference to Its Usefulness in Studies of Peripheral Vascular Diseases, Arch. Int. Med **52**:785 (Nov.) 1933.

44. Scott, W. J. M., and Morton, J. J.: Sympathetic Activity in Certain Diseases, Especially Those of the Peripheral Circulation, Arch. Int. Med. **48**: 1065 (Nov.) 1931.

by warming the extremities, and so they advise in case of doubt as to the efficiency of this method that it be checked against other methods. In some cases of Reynaud's disease and acrocyanosis the increased constrictor tone in response to low environmental temperature is so great that release by this method is not obtainable. In such instances it was found that a slow warming of the parts was obtainable by peripheral nerve block. The procedure, then, is particularly useful in the diagnosis of organic disease and in the determination of the amount of vasoconstriction existing in cases of such disease.

Lewis and Pickering [12] had earlier achieved the same result, perhaps securing even a greater degree of vasodilatation by means of a heat cabinet into which the patient was placed with the hands or feet exposed to a room temperature which was maintained at a lower level (from 16 to 18 C.) than that of the cabinet. With the environmental temperature at a low level a greater rise is secured because of the lower initial starting point. Coller and Maddock [16] used a similar method by placing the patient under a rubber blanket and preventing the elimination of heat from the body as well as increasing the environmental temperature. They were able to secure marked vasodilatation.

When the plethysmograph is used for the measurement of vasodilatation the same extremity may be immersed in water at 45 C. and maximum vasodilatation secured.[41] A similar result can be achieved by the method of Landis and Gibbon,[43] but when it is followed by direct heating of the extremity an even greater increase in the flow of blood is demonstrable.

The release of vascular tone by temporary interruption of the sympathetic pathways to an extremity was first applied to the differential diagnosis of organic and vasospastic arterial diseases almost at the same time by Morton and Scott,[45] White [46] and Brill and Lawrence.[47] They found that with the administration of spinal anesthesia vasoconstrictor tone to the lower extremities could be completely abolished and a marked rise in surface temperature could be measured. The same effect was produced by general anesthesia, and almost identical levels of peripheral cutaneous temperature could be reached in normal persons by either method and no further increase could then be detected. It was assumed that complete inhibition of vasoconstriction occurred, and that maxi-

45. Morton, J. J., and Scott, W. J. M.: The Measurement of Vasoconstrictor Activity in the Lower Extremities, J. Clin. Investigation **9**:235, 1930. Scott, W. J. M., and Morton, J. J.: Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, J. A. M. A. **97**:1212 (Oct. 24) 1931.

46. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to the Extremities with Procaine, J. A. M. A. **94**:1381 (May 3) 1930.

47. Brill, S., and Lawrence, L. B.: Changes in Temperature in the Lower Extremities Following the Induction of Spinal Anesthesia, Proc. Soc. Exper. Biol. & Med. **27**:728, 1930.

mum vasodilatation could be reached with uniformity in different persons.

Lewis and Landis,[48] White,[46] Scott and Morton [44] and others have used the method of peripheral nerve block by local anesthesia for the study and differential diagnosis of vascular diseases.

In the foot, injection into the posterior tibial nerve is easy as it passes behind the internal malleolus at the ankle. In the upper extremity the ulnar nerve at the elbow may be used or the median nerve at the wrist. With complete anesthesia of the cutaneous area corresponding to the distribution of the nerve, the skin temperature in normal persons rises to sufficiently high levels to indicate satisfactory vasodilatation but not quite to that of general or spinal anesthesia.

Scott and Morton [44] consider this a satisfactory method for estimating vasoconstriction but in borderline cases suggest that it be checked with the patient under spinal or general anesthesia. They have established normal levels for vasodilatation for the first toe at 31.5 C. with the patient under spinal and general anesthesia and at 30.5 C. with posterior tibial nerve block if these procedures are carried out at a room temperature of 20 C.

On the basis of this method Scott and Morton were able to divide circulatory syndromes into three main groups, due to (1) occlusion alone, (2) spasm alone and (3) mixed spasm and occlusion. In the first group there is no significant rise in temperature; in the second there is a rise to approximately the normal level for vasodilatation and in the third the response lies between and is significant in proportion to the degree of rise.

The methods of estimating vasoconstrictor tone, particularly peripheral nerve block, have a wide field of usefulness, but it must be borne in mind that normal vasoconstrictor tone as a response to the heat-regulating mechanism of the body should not be confused with pathologic angiospasm.[49] Both are no doubt participants in clinical phenomena.

Oxygen Tension of the Blood.—This has been noted particularly in the study of arteriovenous aneurysms and of erythromelalgia. It is particularly important in the former.

Weiss and Ellis [50] have recently studied the utilization of oxygen and the production of lactic acid by the muscles in the peripheral cir-

48. Lewis, T., and Landis, E. M.: Some Physiological Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, Heart **15**:151, 1930.

49. Lewis, Pickering and Rothschild.[27b] Coller and Maddock.[16]

50. Weiss, Soma, and Ellis, L. B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise in Subjects with Normal and in Those with Diseased Cardiovascular Systems, Arch. Int. Med. **55**:665 (April) 1935.

culation. They found that the degree of loss of oxygen from the arterial blood in relation to the consumption of oxygen of the tissues was one of the best measures of the state of the peripheral circulation. The average level of lactic acid with the patient at rest was likewise found to be uniform in normal persons and in patients with all types of cardiac disease. The utilization of oxygen is normal in persons with cardiac disease also, except in cases of congestive failure. This is due to a reduction in the peripheral circulation.

The more extensive application of these methods to the study of vascular diseases may be of considerable importance.

Arteriography.—In cases of arteriosclerosis visualization of the arteries of the extremities has been of some value in that by its means the presence, and to some extent the degree, of calcification could be determined. No conception can be obtained of the efficiency of the circulation in calcified vessels.[51]

With the introduction of a satisfactory opaque solution, considerable progress has been made. Leriche [52] believes that only one satisfactory agent is available at present, namely, a stable solution of thorium dioxide. While solutions of sodium iodide are satisfactory from a technical standpoint and for the observation of veins, the arterial spasm induced renders them dangerous. He has frequently observed cadaveric pallor in an extremity following its use even with the patient under anesthesia, which is usually necessary because of the severe pain which the intra-arterial injection of this drug often precipitates. With thorium dioxide Leriche has seen no bad results in an extensive experience, and he considers its use in the diagnosis of vascular disease of great value.

A number of reports of accidents in the use of other types of opaque mediums for arteriography have appeared from France.[53]

Allen and Camp [54] have described a satisfactory technic for the use of solution of thorium dioxide with good results. The report of Veal

51. Lansbury, J., and Brown, G. E.: The Clinical Significance of Calcification of the Arteries of the Lower Extremities, Proc. Staff Meet., Mayo Clin. **9**:49 (Jan. 24) 1934.

52. Leriche, R.: Sur la bénignité des artériographies au thorotrast, Bull. et mém. Soc. nat. de chir. **61**:175 (Feb. 16) 1935.

53. Leveuf, Jacques: Les dangers de l'artériographie, Bull. et mém. Soc. nat. de chir. **61**:6 (Jan. 19) 1935. Bazy, L., and Reboul, H.: Etude critique sur l'artériographie, ibid **61**:18 (Jan. 19) 1935.

54. Allen, E. V., and Camp, J. D.: Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance, J. A. M. A. **104**:618 (Feb. 23) 1935; The Value of Arteriography, Radiology **22**:678 (June) 1934.

and McFetridge [55] is essentially the same. The chief value of this method is not for diagnosis only; information is obtained regarding details of circulation in cases of arterial disease not otherwise obtained, particularly in regard to the collateral circulation. In the normal arm and hand the vessels are clearly outlined with a minimum of collateral branches, which in obstructive disease are numerous, particularly in cases of thrombo-angiitis obliterans, in which also the involved arteries usually show a patchy distribution of lesions in various locations, particularly in the palmar and digital arteries of the hand. The contour of the lumen is irregular and varies in size in the initial stages of the disease. The lumen is reduced in size and follows an irregular course, widening and narrowing, often being divided as by an island in a stream. In the final stage complete occlusion of an artery often occurs, with a small channel sometimes extending into an occluded portion.[56]

In arteriosclerosis the extent and degree of the lesions show great variation. The principal arteries and collateral branches are involved. The arterial image looses its curves and regular contours and shows marked tortuosity. The size of the lumen varies and may be thread-like or obliterated. Collateral circulation is conspicuously limited. Segmental obliteration is sometimes seen with the vessel functioning below the point of obstruction.[57]

Information may be gained concerning arteriovenous fistulas, the characteristics of which are dilatation of the arteries leading to the fistula and pooling of the medium in the region of the fistula. Horton [58] was able to visualize an aneurysm involving the femoral artery and vein and thus establish its definite location. Yater and White [59] were able to show the exact location, size and shape of an arteriovenous aneurysm of the ulnar artery.

Veal and McFetridge [55] are of the opinion that in the selection of the location for amputation in a case of gangrene arteriography is of considerable value and is a more reliable indication of adequate collateral circulation than the histamine test.

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55. Veal, J. R., and McFetridge, E. M.: Adequate Circulation in the Extremities, J. A. M. A. **104**:542 (Feb. 16) 1935; Arteriography in Gangrene of the Extremities by the Use of Thorium Dioxide (Stabilized), Ann. Surg. **101**:766, 1935.

56. Knapp, J. C.: Arteriography, N. Y. State J. Med. **35**:76 (Jan. 15) 1935.

57. Contiades, X. L., and Nalleau, J.: Results of Arteriography in Diseases of the Arteries and Tumors, Presse méd. **42**:1866, 1934.

58. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, Am. J. M. Sc. **187**:649 (May) 1934.

59. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, Am. J. M. Sc. **186**:493 (Oct.) 1933.

In regard to the dangers involving the use of solution of thorium dixode, most writers seem to be in agreement. The fact that the metal is not eliminated but remains fixed in the reticulo-endothelial system is recognized. What the delayed effect of the retention of a radioactive substance of this type may be is not known, but until now no harmful effects have been reported.

THROMBO-ANGIITIS OBLITERANS

Although the actual cause of thrombo-angiitis obliterans is still obscure, certain phases of the etiology have been established; so predisposing factors may be considered in a more certain light. The racial factor has been disposed of. The disease has occurred in almost all races. Horton and Brown [60] have observed 10 cases in women in a total of about 700. In addition to these they reviewed the literature on the few cases previously reported. This seems to illustrate the rarity of the disease in the female, and it is worthy of note that all these cases were relatively mild. These authors believe that the disease occurs in women in so mild a form that it is overlooked because few subjective phenomena present themselves. Silbert [61] found only 2 cases in women in over 2,000 and admits a total of only 9 in women among 2,200 reported in the literature. He finds that the disease occurs more frequently in Jews and notes that it has been reported in brothers more frequently than is accounted for by coincidence. This suggests a hereditary sex-linked factor by which the disease may be transmitted through the female to the male offspring.

In regard to the relationship of tobacco, Silbert and his associates [62] say that typical examples of thrombo-angiitis obliterans have not occurred in nonsmokers and that sensitiveness to tobacco is one of the primary factors in its cause. Some other workers are of the opinion that tobacco is not primarily concerned as an etiologic factor but that it is important in influencing the progress and severity of the disease.

There can be no question that cigaret smoking particularly plays a most important, if coincidental, rôle in the disease. The initial effect of nicotine on the sympathetic ganglions has long been known, as well

60. (*a*) Horton, B. T., and Brown, G. E.: Thrombo-Angiitis Obliterans Among Women, Proc. Staff Meet., Mayo Clin. **7**:107 (Feb. 24) 1932; (*b*) Thrombo-Angiitis Obliterans Among Women, Arch. Int. Med. **50**:884 (Dec.) 1932.

61. Silbert, Samuel: Thrombo-Angiitis Obliterans in Women: Report of Two Cases, Ann. Surg. **101**:324 (Jan.) 1935.

62. Harkavy, J.; Habold, S., and Silbert, S.: Tobacco Sensitiveness in Thrombo-Angiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **30**:104 (Oct.) 1932.

as its transient effect on the heart rate and blood pressure. In addition to these, it has been well established that peripheral vasoconstriction occurs in almost all subjects, whether habituated smokers or not, as measured by a decrease in the surface temperature of the extremities.

Maddock and Coller [63] in well controlled experiments showed that in addition to the increase of heart rate and rise in blood pressure there was a consistent fall in surface temperature, greatest in the toes, after the smoking of a cigaret. This fall in temperature lasted until after the other cardiovascular phenomena had returned to normal. They are of the opinion that the effect is directly on the sympathetic nervous system, as it failed to occur in a patient with peripheral nerve block and in a patient on whom sympathetic ganglionectomy had previously been carried out. The effects on the heart rate and blood pressure were the same as those in normal persons. The authors believe this to be an effect of small amounts of nicotine. The degree depends on the rapidity of smoking as well as on inhalation. To corroborate this view they were able to obtain a similar effect by the intravenous injection of nicotine in the amount comparable to what might be obtained by the smoking of a cigaret. The results of this experiment were the same as those produced by smoking on heart rate, blood pressure and peripheral surface temperature.

Johnson and Short [64] think that the main action of smoking is a brief stimulation by nicotine of the sympathetic ganglions, that the rise in blood pressure is by visceral and later peripheral vasoconstriction resulting from stimulation of the adrenal glands through the sympathetic system by nicotine. This is comparable to the rise in blood sugar on smoking noted by Haggard and Greenberg,[65] which they attributed to an increased rate of discharge of epinephrine resulting from stimulation of the sympathetic ganglions.

That the vascular phenomena accompanying smoking are due to combustion of the tobacco and not to the paper of cigarets is further corroborated by Barker,[66] who found that the same effects follow smoking by patients with thrombo-angiitis obliterans as occur in normal persons. The conclusions of Wright and Moffat [67] are in agreement that nicotine is at least one of the important toxic factors and carbon

63. Maddock, W. G., and Coller, F. A.: The Relation of Peripheral Vasoconstriction to Tobacco, Ann. Surg. **98**:70 (July) 1933.

64. Johnson, H. J., and Short, J. J.: Effect of Smoking on Skin Temperature, J. Lab. & Clin. Med. **19**:962 (June) 1934.

65. Haggard, H. W., and Greenberg, L. A.: The Effects of Cigarette Smoking on Blood Sugar, Science **79**:165, 1934.

66. Barker, N. W.: The Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet., Mayo Clin. **8**:284 (May 10) 1933.

67. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral Vascular System, J. A. M. A. **103**:318 (Aug. 4) 1934.

monoxide and the products of paper combustion are not the cause. They found almost the same results with denicotinized cigarets, the content of which is about 40 per cent of the average of standard brands. In addition to the fall in peripheral cutaneous temperature, they found on observation of the capillaries of the nail fold that there was a marked slowing and even stasis of the blood in these vessels after the smoking of a single cigaret. This effect was variable even in the same person at different times, as are the variations in skin temperature, which are most marked in the periphery and which fail to show any comparable change when readings are made on the forehead.

With the idea that allergy might be a factor in thrombo-angiitis obliterans, Harkavy, Habold and Silbert [62] investigated 68 cases and found that in more than 80 per cent there was a reaction to one or more of five tobacco allergens by cutaneous test. Of the control group of 107 patients who were comparable cigaret smokers, 97 gave a negative reaction to all five allergens; 15 of these had atherosclerotic vascular disturbances, and all were heavy cigaret smokers. In 13 of 20 cases passive transfer was accomplished. In their studies Wright and Moffat,[67] although they found positive cutaneous reactions with tobacco and nicotine, were unable to show any relationship to the fall in surface temperature.

Sulzberger [68] found a positive reaction of the skin to tobacco in 78 per cent of 24 patients with thrombo-angiitis obliterans, in 36 per cent of smokers without this disease and in only 16 per cent of nonsmokers. He was unable to demonstrate passive transfer except in 1 case. He was able to demonstrate positive cutaneous reactions to other allergens and inhalants. He concludes that thrombo-angiitis obliterans is usually the result of hypersensitization to tobacco but may also result from sensitization to other allergens and that nicotine plays no allergic rôle.

It must be admitted that the high percentage of positive cutaneous reactions to tobacco in patients with thrombo-angiitis obliterans is significant in contrast to that obtained in normal users of tobacco and in nonsmokers, and it is likewise reasonable to believe that if thrombo-angiitis is an allergic vascular reaction primarily, other factors than tobacco may be the offending agents in nonsmokers. This, however, does not explain the great variation in sex incidence. But, be that as it may, there is little reason to doubt the additional part played in the disease by the toxic action of small amounts of nicotine by inhalation in the production of damaging vasoconstriction in anatomically impaired vessels or in a barely sufficient collateral circulation.

68. Sulzberger, M. B.: Recent Immunologic Studies in Hypersensitiveness to Tobacco, J. A. M. A. **102**:11 (Jan. 6) 1934.

Jäger [69] as a result of his careful pathologic studies of this disease believes that there is a generalized reaction of the intima as the initial lesion; he mentions allergy as well as a specific bacterial or other intoxication as a possible factor which secondarily brings about thrombosis.

Certainly, whatever the primary cause may be, the idea of infection seems unlikely. The innumerable bacteriologic studies of the blood and excised thrombi of vessels have all been fruitless. Buerger [70] was unable to reproduce the vascular lesion even by the injection of thrombotic material from a patient with migrating phlebitis into the ligated vein of another person. He was able to reproduce a lesion locally by applying the clot so removed under and to the side of a ligated vein with the scrapings of the intima applied to the adventitia. In from ten to twelve days the characteristic histologic changes of thrombo-angiitis obliterans occurred. This is the only evidence of infection.

It has been suggested [71] that trauma, minor infections and exposure to cold to which the extremities are subject are factors which predispose to thrombosis in the peripheral vessels as well as tobacco. Since the visceral vessels are not concerned with the regulation of temperature by conservation of heat and are not subject to the extremes of environmental change, thrombosis does not so readily develop there.

The relationship of this disease to endocrine disturbances has been suggested, and the parathyroid glands, because of the elevation of the calcium content of the blood, have been suspected. Bastai and Dogliotti [72] performed partial parathyroidectomy in 5 cases with lowering of the calcium content of the blood, immediate cessation of pain and healing of wounds previously resistant to treatment. The significance of this work and that of others remains to be seen.

Pathology.—The pathologic picture presented in the stage of thrombosis or later has been the basis for the opinion that thrombo-angiitis obliterans is an inflammatory disease of infectious origin. The typical pathologic change in the peripheral vessels is so well known that there is no need of repeating the description here.

The most important recent advance in the knowledge of the pathologic process is brought to light in the excellent studies of Jäger.[69] In

69. Jäger, Ernst: The Pathologic Anatomy of Thrombo-Angiitis Obliterans in Juvenile Gangrene of the Extremities, Virchows Arch. f. path. Anat. **284**:526, 1932.

70. Buerger, Leo: Thrombo-Angiitis Obliterans: Experimental Reproduction of the Lesions, Arch. Path. **7**:381 (March) 1929.

71. Taube, N.: Mesenteric Involvement in Buerger's Disease, J. A. M. A. **96**:1469 (May 2) 1931.

72. Bastai, P., and Dogliotti, G. C.: Hyperparathyroïdie et syndrome angiospastique, Presse méd. **42**:1761 (Nov. 10) 1934.

addition to the usual findings he was able to demonstrate a general intimal reaction extending far beyond the location of the active lesions. This he says is the fundamental initial type of lesion. It consists of a cushioning of the intima with the development of nodular raised areas, exudative and proliferative and containing giant cells. These foci are somewhat similar to the Aschoff body of rheumatic fever. In fact, Jäger states that the pathologic process of thrombo-angiitis obliterans in the large arteries resembles that of rheumatic fever; in the medium-sized arteries, that of vegetative endocarditis, and in the small arteries, periarteritis nodosa.

Telford and Stopford [73] have recently advanced the theory that the initial lesion in thrombo-angiitis obliterans is intimal proliferation followed by thrombosis and atypical organization in the medium-sized arteries of the legs. They believe that vascular spasm is primary and the intimal changes are the result. They point out that they have found that the thrombosis and fibrosis which involve the perivascular structures extend beyond the intimal proliferation, which may be limited to a very small area.

Morgan [74] says that the lesion may be present in any of the large arteries or veins and may originate in any part of an artery with or without involvement of the adjacent venae comites. The lesion may begin in a vein without a similar condition in the adjacent artery. The initial lesions begin in one or more isolated areas and later progress from one or more foci to the chronic stage with irregular scattered lesions.

Evidence at autopsy of involvement of visceral arteries in cases of peripheral thrombo-angiitis obliterans has been reported by a number of observers. Taube,[71] with a report of 2 additional cases, reviews the literature. The diseased vessels included the aorta, the coronary arteries and the mesenteric, renal, spermatic, celiac axis and cerebral arteries, usually in combination. Averbuck and Silbert [75] reported on the cause of death in 47 cases of typical thrombo-angiitis. There were autopsies in 19. In 22 the patient died of a vascular accident, and in 18, of coronary thrombosis. The authors point out that the findings in the visceral vessels were not always characteristic of the disease; even in a patient aged 24 there was arteriosclerosis of the coronary arteries. The authors are of the opinion that the vascular involvement of the visceral vessels bears a definite relation to the peripheral disease.

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73. Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. **1**:863 (April 27) 1935.

74. Morgan, J. R. E.: Distribution of the Lesions of Thrombo-Angiitis Obliterans in the Vessels of the Leg, Arch. Path. **18**:216 (Aug.) 1934.

75. Averbuck, S. H., and Silbert, S.: Thrombo-Angiitis Obliterans: The Cause of Death, Arch. Int. Med. **54**:436 (Sept.) 1934.

Allen and Willius [76] reported 7 clinical cases of coronary disease in 225 living patients and are of the opinion that it is not a significant number.

Birnbaum, Prinzmetal and Connor [77] report a case of generalized vascular disease in which clinically the picture was that of multiple thrombosis involving the mesenteric as well as the peripheral vessels, finally terminating with bilateral adrenal infarction. The pathologic findings, while not typical in all essentials, resembled those of thrombo-angiitis obliterans more nearly than those of any other vascular disease. There was no clinical peripheral arterial involvement, and it was the authors' impression that adrenal infarction caused death before the typical manifestations of the disease became evident.

In a case reported by Telford and Stopford,[73] that of a man 26 years of age, the condition terminated in sudden death by coronary thrombosis. The pathologic changes in the coronary arteries were indistinguishable from those of typical thrombo-angiitis obliterans.

In the 5 cases reported by Jäger [69] the general involvement was typical of the disease, the blood vessels of the brain, heart, kidneys, liver, spleen, stomach and lungs being involved in typical fashion. He concludes that the disease is not limited to the vessels of the extremities but attacks the entire vascular system.

Thus, it seems that extensive visceral involvement does occur at least in a certain number of cases. It is certainly true that these comprise only a small portion of the total number of cases of the disease, and, clinically at least, thrombo-angiitis obliterans must be considered essentially a disease of the peripheral arteries.

Clinical Syndrome.—This has been so completely described by Buerger [23] and others that little has been added. The symptomatology is dependent on the impairment of arterial circulation, migrating phlebitis or their complications. The pain of intermittent claudication is usually the initial symptom, although fatigue in the muscles of the legs and coldness of the extremities with vasospastic symptoms, particularly in the hands, suggesting the Raynaud syndrome are not uncommon. Trophic ulcers, superficial phlebitis or even sudden arterial occlusion may be the presenting symptoms.[51a] It has been suggested that even though these are the initial symptoms the disease has been progressing for months or years before becoming evident.[73]

76. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated with Thrombo-Angiitis Obliterans of the Extremities, Ann. Int. Med. **3**:35, 1929.

77. Birnbaum, W.; Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-Angiitis Obliterans: Report of a Case with Involvement of Retinal Vessels and Suprarenal Infarction, Arch. Int. Med. **53**:410 (March) 1934.

The pain which occurs is usually of two types: (1) pain that is induced by exercise or (2) that which occurs while the patient is resting. The former is the well known intermittent claudication usually considered the result of muscular ischemia, rarely of phlebitis.[78] Pain while the patient is resting may precede ulceration or gangrene. It is continuous, often worse at night and aggravated by change in posture; after gangrene or ulceration appears the deep burning pain may change to superficial burning. Secondary infection may be a dominant factor even to the extent of formation of abscesses.[79] With phlebitis or arteritis the pain is less severe and is generalized or aching, while with arterial occlusion it is sudden and severe and radiates peripherally. The pain which accompanies ischemic neuritis is severe and diffuse, covering large areas, does not correspond entirely to nerve distribution and is paroxysmal and often lancinating.

Variation in color with change in position has been described previously, and examination by various methods demonstrates impairment of arterial circulation, usually in more than one extremity.[73]

The general opinion is that this disease runs a chronic course of varying duration and then tends to stop progressing and becomes healed. Collateral circulation is extensive and if it is adequate may restore the extremity to usefulness with a minimum loss of tissue.

Brown [31a] recognizes five clinical types: 1. In the compensated type the disease is of long duration, trophic changes do not occur, and adequate collateral circulation has developed. Fatigue and mild claudication are the important symptoms. 2. In the slowly progressive type symptoms and signs of arterial occlusion are evident, with pain and reduced surface temperature. Improvement is followed by relapses. The collateral circulation keeps pace fairly well with the occlusive process.

3. Limited areas of gangrene occur with superficial ulcers of the digits, and pain while the patient is at rest occurs during the active stages of ulceration. The collateral circulation is nearly adequate, and no large amount of tissue is lost. The ulcers are induced by trauma, unnecessary surgical intervention or the application of antiseptics.

4. In the acute progressive type there is the picture of extensive arterial occlusion, with rapid development, severe claudication and severe pain while the patient is at rest and the appearance of gangrene and larger ulcers.

78. Goldsmith, Grace A., and Brown, G. E.: Pain in Thrombo-Angiitis Obliterans, Proc. Staff Meet., Mayo Clin. **9**:201 (April 4) 1934.

79. Samuels, S. S.: Thrombo-Angiitis Obliterans with Secondary Abscess Formation in the Extremities, M. Rec. **139**:116 (Feb. 7) 1934.

5. The extreme type with massive gangrene often occurs as the end-stage of the preceding types. In addition, there are a few distinct variations from this main grouping.

In studies of the capillaries in this disease two general types of reaction of the capillaries have been noted.[80] There is one in which the capillaries are dilated and the majority are filled and visible. The flow is slow. With dependence of the extremity and the development of cyanosis more of these vessels open, and the flow of blood is still more retarded. In the second type, with phenomena of vasoconstriction, the reaction is similar to that of Raynaud's disease. Constriction of the capillaries is noted, and only a few are visible. The flow is slow and the blood cyanotic. With an increase in temperature there are more vessels to be seen, and the rate of flow increases slightly but is jerky and intermittent. The vessels are not paralyzed, since they respond to epinephrine and histamine locally. Many are actually found to be thrombosed.

Rabinowitch [81] provides an interesting concept of the rôle of the smaller vessels in cases of thrombo-angiitis obliterans. In the early stages of the disease there is increased irritability of the capillaries, so that vasospastic symptoms may be present with rapid changes in capillary tone and symptoms often mistaken for those of the Raynaud syndrome. This would be compatible with the second type of reaction of the capillaries described earlier. In the second stage the vasospastic tendency gives way to a complete loss of capillary tone with dilatation and failure to respond to stimuli corresponding to the first type. The foot or hand is cold, and the color is dusky red. The color depends on the state of dilatation of the cutaneous vessels and not on the rate of blood flow through them. The lowered surface temperature is due to the occlusion of the larger arteries by thrombosis. In the third stage of impairment of the capillaries stasis and thrombosis occur. Gangrene, the author thinks, does not often affect a large area at one time as it does in arteriosclerosis. Small areas of necrosis occur as a superficial ulcer or ecchymotic spot which may gradually spread to involve a whole toe. At the same time similar areas form elsewhere in the adjacent tissue, and the process then gradually spreads until larger areas may be involved.

The cause of these alterations in the capillaries is explained on a metabolic basis. Lecithin is mobilized from the tissues to the blood with the retention of degradation products, such as choline and its derivatives. This is responsible for the lesions of the capillary beds and the thrombotic tendency. The urine of patients contained choline in most

80. Wright and Duryee.[3] Brown, Allen and Mahorner.[25]

81. Rabinowitch, I. M.: Newer Concepts on the Physiopathology and Treatment of Thrombo-Angiitis Obliterans, Am. J. Surg. **21**:260 (Aug.) 1933.

instances in considerable quantity, while the urine of controls did not. There is an increase in the lecithin content of the blood, which may account for the tendency to coagulation.

The abnormal deprivation of the tissues of lecithin is probably also responsible for the absorption of myelin which has been noted by Brown, Allen and Mahorner.[25] This has a bearing on the increased irritability of sensory nerves in the part affected and is the explanation offered for the severe intractable pain in the pregangrenous and gangrenous stages of the disease.

In their studies on the chemistry of the blood Friedlander and Silbert [82] make no mention of lecithin. They did find the values for cholesterol elevated consistently, as were those for total ash, total protein and calcium, while the values for the chlorides and sugar were normal. Decreased blood volume [83] and a low basal metabolic rate [84] have also been recorded. Koukine [85] reports the viscosity and coagulation time of the blood to be increased and the number of thrombocytes decreased, which is not in accord with the observations of others. There is so little agreement, however, in regard to alteration of the chemical composition of the blood [25] in cases of thrombo-angiitis obliterans that the only conclusion that can be drawn in regard to these findings is that they are variable.

It is agreed that arteriosclerosis is frequently found in association with thrombo-angiitis obliterans,[86] even in relatively young patients. This offers some difficulty in diagnosis in the cases in the older age groups. The increased element of vascular spasm has been pointed to as a distinguishing feature, and also the much greater collateral circulation in thrombo-angiitis obliterans. The presence of arteriosclerosis in other vessels and the demonstration of the presence of calcification by roentgen examination, while not conclusive,[51] are of importance.

In reporting on the occurrence of diabetes as a complication in 4 cases of thrombo-angiitis obliterans, Horton and Allan [87] comment on the rarity of the association of these two disorders in contrast to the

82. Friedlander, Mae, and Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): VI. Chemistry of the Blood, Arch. Int. Med. **48**:500 (Sept.) 1931.

83. Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans, M. Rec. **97**:430, 1920.

84. Silbert, S., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans (Buerger): Basal Metabolism, J. A. M. A. **96**:1857 (May 30) 1931.

85. Koukine, N.: Problems of the Etiology, Clinical Findings and Treatment in Endarteritis Obliterans, Rev. de chir. **53**:639, 1934.

86. Barron, M. E., and Lilienthal, H.: Thrombo-Angiitis Obliterans: General Distribution of the Disease, Arch. Surg. **19**:735 (Oct.) 1929. Averbuck and Silbert.[75]

87. Horton, B. T., and Allan, F. N.: Thrombo-Angiitis Obliterans in Patients with Diabetes, Ann. Int. Med. **7**:799 (Jan.) 1934.

relationship of diabetes to arteriosclerosis. It is interesting to note that in these cases the disease did not seem to be accentuated by the presence of diabetes.

ESSENTIAL THROMBOPHILIA

Nygaard and Brown [88] reported 5 cases in which thrombosis occurred in cyclic phases. Both arteries and veins were involved, with a widespread distribution of lesions. The cerebral, retinal and other visceral arteries as well as the arteries of the extremities were involved. The veins in which thrombosis developed were mainly those of the lower extremities. The clinical course was stormy, and death from vascular occlusion occurred in 2 cases. The onset was abrupt in apparently healthy persons.

The pathologic changes consisted of a nonreactive type of thrombosis with occasionally a slight reaction in the arterial wall. There was no evidence of arteriosclerosis in the walls of the vessels, nor could the pathologic picture be identified with that of thrombo-angiitis obliterans.

One characteristic was outstanding in all the cases. During the thrombosing phase of the disease and for a considerable period afterward there was a definite increase in the coagulation of the plasma. There were no consistent variations in the albumin-globulin ratio or in the platelet counts. In 50 cases of thrombo-angiitis obliterans and arteriosclerosis with occlusion there were no deviations from the normal in respect to these three tests.

As the authors suggest, cases of this type of what they believe to be a distinct clinical entity are most likely to be considered cases of thrombo-angiitis obliterans. This type of disorder might account for some of the unexplained cases of venous thrombosis as well as of visceral thrombosis in the absence of infection or of degenerative vascular disease.

ARTERIOSCLEROSIS

The term arteriosclerosis is used to include all types of degenerative arterial disease. It is becoming a generally accepted idea that this condition represents a disease process to which older persons are usually most susceptible. Under certain conditions, particularly in cases of diabetes, an identical type of arterial disease occurs in young persons. Its manifestations vary in different persons as well as in different locations in the body.

The whole subject is so well covered in a publication edited by Cowdry [89] that it is useless to attempt more than the briefest discus-

88. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia (Thrombosing Disease), Proc. Staff Meet., Mayo Clin. **10**:13 (Jan. 2) 1935.

89. Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933.

sion here. The relationship of cholesterol to atherosclerosis is reviewed in detail by Anitschkov in Cowdry's volume. In regard to his comparison of observations on the experimental production of atherosclerosis in the rabbit, with his observations on the disease in man, Leary [90] draws the following conclusions from the study of the coronary arteries: Atherosclerosis is a disease and not the consequence of age, since it appears in the young and is selective in location. The characteristic lesion in youth is fibrosis associated with the presence of lipoid cells which do not appear in large numbers because of the reaction of the fibrous tissue. Thrombosis occurs when there is necrosis which reaches the endothelium from the subendothelial layer. The characteristic lesion in older persons is the accumulation of large collections of lipoid cells with little connective tissue support. As a result of poor nutrition necrosis occurs and so-called atheromatous abscesses develop. The process is primary in the intima. Stresses favor the location of lesions in the elastica and secondarily in the media. The disease can be reproduced by feeding cholesterol to rabbits. The fibrosis which is characteristic of the coronary lesions in young persons is the characteristic cholesterol atherosclerosis of young rabbits. Fibrosis is the reaction of youth, not of species.

Leary [90] is of the opinion that atherosclerosis is a disease of cholesterol metabolism comparable to diabetes. He is in agreement with Anitschkow [91] that the thyroid gland seems to control in some way the experimental production of atherosclerosis.

Rabinowitch,[92] in a study of the question in diabetes, was led to believe that excess cholesterol in the blood is an important etiologic factor in the production of arteriosclerosis in the young person with diabetes. He is in agreement with Leary,[90] Joslin [93] and others that diets high in fat promote the early development of arteriosclerosis and concludes that treatment with a diet high in carbohydrate and low in calories has delayed the development of cardiovascular disease in the cases investigated.

The intimal types of arteriosclerosis, whether essentially atherosclerotic or fibrotic, would seem, then, to have the same causative background, and according to Leary [90] to be merely the difference in response to age. Several other factors of importance should be mentioned, among them the location of the disease process and the type

90. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary Atherosclerosis), Arch. Path. **17**:453 (April) 1934.

91. Anitschkow, N.: Experimental Arteriosclerosis in Animals, in Cowdry,[89] p. 271.

92. Rabinowitch, I. M.: Arteriosclerosis in Diabetes: I. The Relation Between Plasma Cholesterol and Arteriosclerosis; II. Effects of the High Carbohydrate Low Caloric Diet, Ann. Int. Med. **8**:1436 (May) 1935.

93. Joslin, E. P.: Fat and the Diabetic, New England J. Med. **209**:519, 1933.

of vessel involved.[94] In the large arteries of the elastic type, including the aorta and the main branches, the intimal type of lesion is the only type essentially atheromatous or fibrotic, with lipoid-containing cells. In the large muscular arteries of the extremities, including the radial and ulnar artery and those of the leg, the picture is variable.

It is here that the Mönckeberg sclerosis [94] is characteristic. It is a primary involvement of the media with necrosis and calcification and is usually considered to be unassociated with the intimal type of arteriosclerosis, although the two conditions may occur simultaneously. The arteries are converted into solid tubes with calcareous material deposited in ring-shaped masses, producing the characteristic goose-neck arteries. This type of disease is associated in pathologic appearance with that produced by the repeated intravenous injection of epinephrine in rabbits. This is in contrast to the intimal atherosclerotic type resulting from feeding of cholesterol. The Mönckeberg type of sclerosis has little effect on the efficiency of circulation. It is in the intimal type that impairment occurs.

In cases of arteriosclerotic gangrene the arteries of the lower extremities show advanced sclerosis with progressive obliteration of the lumen.[89] The intima shows thickening by the development of collagenous fibrous tissue. This thickening is irregular, and the narrowed lumen may be situated eccentrically. In the deeper layers of the intima there are areas of fatty degeneration and necrosis with the deposits of cholesterol crystals. The process may extend into the media or even to the adventitia, which may be fibrosed. The arteries become extensively calcified with deposits of calcareous material at the line of the intima and media. When the process invades the endothelial layer of the intima thrombosis occurs, which finally brings about complete occlusion of the vessel.

In cases of diabetes the problem is similar except that arteriosclerosis usually becomes evident at a much earlier age. Rabinowitch [95] states that five years is the usual time necessary for its development, regardless of age. He quotes Shields-Warren and Joslin in regard to the frequency of this condition in children with diabetes. Arteriosclerosis is appreciably affecting mortality. The severity of the diabetes is not connected, and most "vascular deaths" in cases of diabetes result from cardiac disease or gangrene of the extremities. By means of a combined method of examination the incidence of arteriosclerosis in 500 diabetic persons was estimated as 62.6 per cent, a much greater incidence than that obtained by single methods of examination and

94. Ophüls, William: The Pathogenesis of Arteriosclerosis, in Cowdry,[89] p. 249.

95. Rabinowitch, I. M.; Ritchie, W. L., and McKee, S. H.: A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus, Ann. Int. Med. **7**:1478 (June) 1934. Rabinowitch.[92]

corresponding more nearly to the observations at autopsy. The combined method for the detection of vascular sclerosis was: (1) clinical examination, including the findings of cardiac enlargement, accentuation of the aortic second sound, hypertension and thickening of the vessels; (2) examination of the fundi for sclerosis; (3) roentgen examination of the heart, and (4) examination of the extremities for calcification of the peripheral vessels.

The so-called hyperplastic or diffuse type of arteriosclerosis, which involves primarily the smaller arterial branches and the arterioles, is somewhat confusing. It has been described as endothelial proliferation with hyaline degeneration and, later, fibrosis. The process may readily go on to complete occlusion. It is usually associated with hypertension and is said to occur infrequently in the muscular arterioles.[96]

Graham [97] states that in the smaller branches of the arteries of the extremities intimal thickening occurs primarily with fibrosis in the so-called senile type of arteriosclerosis. It produces partial occlusion or obliteration of the distal smaller branches. Atrophy of the skin and muscles follows as a result of impairment of their nutrition by these vascular changes.

With such impairment of circulation in the smaller vessels repeated minimal traumas are emphasized as the factors appearing to be the cause of the local development of gangrene involving one or more toes or a small part of the foot. If the trauma is more severe or if infection takes place, thrombosis of the partially occluded arteries follows, and more extensive gangrene is the result.

With the occlusion of a large artery the distal parts become pale or cyanosed, and a large area of gangrene is the result.

Because of the impairment in the smaller arterial branches, collateral circulation is usually poor. In this respect the occlusion in cases of arteriosclerosis differs from that in cases of thrombo-angiitis obliterans and in cases of diabetic arteriosclerosis in younger persons, in whom the obliterating process involves the larger main vessels, leaving the smaller arteries intact for the establishment of collateral circulation. This is not true of diabetic arteriosclerosis developing in older persons who already have well developed arteriosclerosis.

Reid [22] comments on these facts and points out that many persons have marked obliterating arteriosclerosis with absence of pulsations and loss of heat who get along well with a narrow margin of safety unless as a result of exposure to cold, injury, infection or sudden arterial occlusion the circulation becomes totally inadequate and gangrene

96. Bell, E. T.: Arteriosclerosis of the Abdominal Viscera and Extremities, in Cowdry,[89] p. 473.

97. Graham, D.: Chronic Arterial Occlusion of the Extremities, Ann. Int. Med. 7:431 (Oct.) 1933.

results. He emphasizes three important facts: 1. Cold, injury and infection often produce demands with which a reduced circulation cannot cope. 2. Gradual occlusion of the peripheral vessels may not show symptoms, while sudden or rapid occlusion, often accompanied by vasospasm, leads to gangrene. 3. An affected extremity may show by tests a better circulation than a symptomless one.

The clinical phenomena are those dependent on circulatory impairment. In addition to nutritional changes in the skin and muscles with atrophy or impairment of the tissues, there are often increasing intolerance to cold, acroparesthesia, fatigue and aching pains with exercise. Cramping pains at night are more common than typical intermittent claudication which occurs less frequently in cases of arteriosclerosis than in cases of thrombo-angiitis obliterans, probably because the larger vessels are not closed and the obliterating process is in the smaller branches.[97]

The same methods of investigation and diagnosis are applicable as in other types of obstructive disease. The vasospastic phenomena are seldom met. Definite information as to calcification of the peripheral arteries may be gained by roentgen examination. Lansbury and Brown [51] found calcified vessels in 65 per cent of men and 28 per cent of women more than 50 years of age. The presence of calcification furnished no information as to the state of the circulation. They concluded that roentgen study is of limited value in distinguishing cases of thrombo-angiitis obliterans from those of arteriosclerosis obliterans.

In regard to the histamine test, Starr [98] has found that in addition to its diagnostic value in cases of arterial occlusion special significance may be placed on it in cases of diabetes from the standpoint of prognosis. Of the patients in the group studied, none having a normal reaction to the histamine test showed any circulatory disturbance of the feet after a period of five years. Of 32 patients in whom the reaction was impaired, only 5 survived the five year period without serious disturbance. Starr concludes that by means of the test and physical examination persons with diabetes can be divided into three groups: (1) those not threatened with peripheral vascular disease, (2) those in an intermediate group and (3) those in whom extraordinary precautions must be taken to prevent the development of serious disturbance in the feet.

ARTERIAL EMBOLISM

Sudden acute arterial occlusion in the peripheral arteries produces such a clearcut clinical syndrome that there is little difficulty in its recognition. Embolism is the usual cause. The embolus is usually

98. Starr, I., Jr.: The Value of the Cutaneous Histamine Reaction in the Prognosis of Pedal Lesions in Diabetes Mellitus, Am. J. M. Sc. **188**:538 (Oct.) 1934.

released from a thrombus in the left ventricle. Rheumatic cardiac disease [99] and bacterial endocarditis are frequent antecedents. Auricular fibrillation is often present, and embolism may occur with the restoration of a normal mechanism.[100] Rarely, a thrombus in one of the larger arteries may be the source. Paradoxical embolism may occasionally occur.

Pearse [101] briefly describes the condition. He states that almost without exception embolism occurs at the bifurcation of a vessel or at the origin of one of its larger branches.

Pain is the outstanding symptom. It is extremely severe, is sudden in onset and starts at the site of the embolism but soon involves the entire extremity distally. Occasionally the pain may be late and become intense one or even two hours after the onset. It is rarely mild or absent.

Locally, the characteristic findings are pallor, decreased cutaneous sensitivity, loss of heat, reduction or absence of reflexes and paralysis. The changes of color are variable. At first the skin is waxy or cadaveric. This pallor gradually shifts to dark blue cyanosis in the distal part, while the proximal surface presents a blotchy discoloration. In the later stages the hand or foot may become shrunken. In some instances, when the collateral circulation is good there may be few changes in appearance, and spontaneous recovery has been reported even when some superficial gangrene has occurred.[100] On the other hand, the extension of thrombosis above or below the point of embolism may result in extensive impairment of circulation.[102]

Allen and McLean [103] believe that the profound ischemia which follows sudden arterial occlusion is far too marked to be explained by the obstruction of the lumen by the embolus alone. The phenomena which follow are explainable by the theory that widespread arterial spasm occurs involving the occluded vessel and its branches. They quote Seifert, who observed arterial spasm at embolectomy and who concluded that the pain was due to extensive arterial spasm. This view, they state, is also in accord with the experimental work of Gosset, Bertrand and Patel as well as with that of Mulvihill and Harvey.

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99. Weiss, Soma, and Davis, D.: Rheumatic Heart Disease: Embolic Manifestations, Am. Heart J. **9**:45 (Oct.) 1933.

100. Brust, R. W.: Embolism of the Peripheral Arteries, J. A. M. A. **102**: 2172 (June 30) 1934.

101. Pearse, H. E., Jr.: Embolectomy for Arterial Embolism of the Extremities, Ann. Surg. **98**:17 (July) 1933.

102. Danzis, M.: Arterial Embolism, Ann. Surg. **98**:422 (Sept.) 1933.

103. Allen, E. V., and McLean, A. R.: Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride: Report of a Case, Proc. Staff Meet., Mayo Clin. **10**:216 (April 3) 1931.

SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

De Takáts [104] comments on the confusion of the various types of vascular reactions caused by specific agents which are often confused with thrombo-angiitis obliterans. He is of the opinion that this disease picture will eventually be divided into several types of specific disease etiologically. Endothelial proliferative reactions are similar in a variety of conditions and are characterized histologically by cushions of cellular masses which accumulate beneath the endothelium, alter the permeability of the wall of the vessel and are responsible for other changes, such as medial edema, perivascular reactions, thrombosis and even perineuritis. This vascular response is typical of many types of damage, including frost-bite, reaction to electrical discharges and chemical injuries as well as bacterial and allergic reactions. He refers in this view to the work of both Gruber [105] and Hellmuth.[106]

Mathieu, Colleson and Chaltus [107] have recently reported 6 cases of arteritis in association with gout. Acute arteritis of the extremities has been reported during the course of typhoid, influenza, cholera, scarlet fever and rheumatic fever.[22] Reid states that tuberculosis of the peripheral arteries is rare. The arteries may become involved by direct extension from a nearby lesion or more rarely by infected emboli. Tuberculosis occurs more frequently in the visceral vessels. One case of gangrene of an extremity was reported by Bäumler which was caused by tuberculosis of the peripheral arteries.

Baumgarten and Cantor [108] in reporting a case of tuberculous mesarteritis with aneurysm of the femoral artery make the statement that tuberculous arteritis as a result of direct extension from a tuberculous process to the small arteries of an organ has no clinical importance other than that of involvement of the organ. It is merely part of the general disease, and involvement of the walls of the vessels under these conditions is of no special importance regardless of the location.

The involvement of large or medium-sized arteries is a rare but important type of vascular disease, as the media is usually involved and aneurysm is the result. Baumgarten and Cantor found only 20 cases reported previously. Their case is the fifth in which arteritis

104. de Takáts, Géza: Peripheral Vascular Disease, J. A. M. A. **104**:1463 (April 27) 1935. de Takáts and Mackenzie.[26a]

105. Gruber, G. B.: Endarteritis obliterans und Kältebrand, Beitr. z. path. Anat. u. z. allg. Path. **84**:155, 1930.

106. Hellmuth, Margot: Ueber Gefässveränderungen bei der Frostgangrän, Arch. f. klin. Chir. **158**:702, 1930.

107. Mathieu, L.; Colleson, L., and Chaltus, R.: Gouty Arteritis Obliterans, Ann. de med. **35**:124 (Feb.) 1934.

108. Baumgarten, E. C., and Cantor, M. O.: Tuberculous Mesarteritis with Aneurysm of the Femoral Artery: Report of a Case, J. A. M. A. **100**:1918 (June 17) 1933.

was the result of transmission of the tubercle bacilli through the vasa vasorum into the media of the wall of the vessel. Of these 5, the femoral artery was involved in 4.

Barnard [109] in a recent contribution makes similar comment concerning the frequency of involvement by direct extension to the wall of a vessel from without and its infrequent occurrence by other routes. In the case which he describes the internal carotid and coronary arteries were involved. There was no evidence of spread from adjacent foci. The intima showed hypertrophy and edema, but the media was principally involved by infiltration by granulation tissue consisting of epithelioid cells, lymphocytes, plasma cells, fibroblasts and giant cells. In this granulation tissue were areas of necrosis of varying size. The muscle tissue of the media was largely destroyed in the areas involved. The patient died of cardiac disease.

In regard to the effect of syphilis on the peripheral vessels there has been some variation of opinion. Cerebral syphilitic vascular disease is well recognized, and no comment is needed as to the part of this disease in the large arteries. That it does attack the medium-sized and smaller muscular arteries there can be little doubt. Hermann [110] in an excellent paper on this subject comments on the difficulty of decision as to the etiology of vascular disease in the presence of syphilis because even adequate treatment may have little or no effect in the restoration of an already impaired circulation. He gives Warthin's descriptions of the involvement of the smaller arteries. The lesion may appear as panarteritis, periarteritis or proliferating endarteritis. Small arteries showing proliferating and obliterating endarteritis often show extensive perivascular collections of plasma cells, and in these exudates the organism has been demonstrated. There is often secondary degeneration of the intima with fibrosis which develops slowly, usually as a result of impairment of nutrition resulting from involvement of the vasa vasorum in vessels of this class as well as in the aorta. Arteriosclerosis and the syphilitic process are so closely associated in many cases that differentiation is impossible.

Clinically Hermann describes three distinct types of the disease: In the first, angiospastic phenomena are predominant. He thinks that chronic irritation of the perivascular nerve plexuses gives rise to these reflex vasomotor disturbances, which take the form of chronic vasospasm of the peripheral arterioles. The angiospasm disappears with treatment, but whatever organic impairment exists before is unimproved. The second is the endarteritic type, in which the essential lesion is panarteritis or proliferating endarteritis involving the arterioles.

109. Barnard, W. G.: Tuberculous Arteritis, J. Path. & Bact. **40**:433 (May) 1935.

110. Hermann, L. G.: Syphilitic Endarteritis, Am. J. Syphilis **17**:305, 1933.

It is the most common form of syphilitic arteritis. Active antisyphilitic treatment will usually arrest the progress of the inflammatory disease, but restoration of circulation does not follow. The spontaneous development of an efficient collateral circulation is one of the characteristic features of this type of the disease. It is often adequate for the maintenance of integrity of the tissue, but not always for unlimited function.

The third type is the thrombo-arteritic, characterized by thrombosis of the medium-sized and smaller vessels. This is rather an uncommon type of lesion with syphilis. The symptoms in the case reported by Hermann were similar to those often encountered in cases of thromboangiitis obliterans, with pain the predominant complaint. The main arteries of the lower extremities were occluded, but a fairly effective collateral circulation was present. Marked improvement followed antisyphilitic treatment, and collateral circulation was further benefited by positive and negative pressure treatment.

It should be noted that in all three types of syphilitic disease of the peripheral vessels a spontaneous collateral circulation is one of the outstanding features.

Derick and Hass [111] in a recent article describe a case of widespread chronic inflammatory arteritis which they ascribe to syphilis. The small arteries were involved exclusively, and the inflammatory process involved all three coats of the vessels. The arteries were occluded often by proliferative endarteritis or by thrombosis, usually both. Infarction took place in the viscera, where the lesions were extensive and had apparently developed. The relationship of syphilis to the etiology of this case is not conclusive.

Types of arteritis appear occasionally which are reported as atypical. This has been particularly true in some of the reports of cases of periarteritis nodosa.

Barker and Brown [112] report an unusual case of progressive disseminated obliterating arteritis which they were unable to classify. Some of the clinical phenomena were suggestive of periarteritis nodosa, but the pathologic picture was not compatible. The findings were simple endothelial proliferation of the type of obliterating endarteritis which has been described as nonspecific and resulting from a variety of causes. The extraordinary feature of this case was the clinical course, which the authors summarize. The initial symptoms were those characteristic of a typical Raynaud syndrome involving the hands, and they were treated successfully by sympathectomy. Six months later chills and fever developed, which continued irregularly for five months,

111. Derick, C. L., and Hass, G. M.: Diffuse Arteritis of Syphilitic Origin, Am. J. Path. **11**:291 (March) 1935.

112. Barker, N. W., and Brown, G. E.: Progressive Disseminating Obliterating Arteritis of Unknown Origin, M. Clin. North America **16**:1313 (May) 1933.

until death occurred. Neuronitis occurred in all four extremities, with some evidence of additional cerebral involvement. There were scattered digital and cutaneous vascular lesions with infarction. Diarrhea and abdominal cramps with blood in the stools occurred in episodes, as well as renal involvement.

Horton, Magath and Brown [113] report 2 cases of arteritis of the temporal vessels with similar clinical and pathologic pictures. Localized periarteritis and arteritis were demonstrable and seemed to be identical in the 2 cases. Relapses and remissions occurred in each. Recovery took place finally. Cultures of the excised vessels and pathologic studies failed to reveal a cause. The similarity of the pathologic findings in these cases as well as the similar course suggested a definite disease type which the authors think might be sufficiently characteristic to represent a disease entity, although they have not found corresponding reports in the literature.

Periarteritis nodosa has been considered a rare disease. Haining and Kimball [114] report a case to be added to the 150 previously reported, 20 of which these authors say are in the American literature. The disease is seldom diagnosed clinically, and it must be frequently overlooked since its phenomena in fatal cases may often be cardiac or renal and are classified as cardiac or renal disease. Although it is usually considered to be fatal, apparently some patients survive the acute stage. One of Arkin's [115] patients lived for four years after the acute attack, and the disease process was then found to be healed on histologic examination.

Periarteritis nodosa is an arterial disease [114] involving the medium-sized vessels and often their smaller branches. Secondary changes in the structure supplied occur as a result of circulatory impairment.

The typical gross pathologic change [116] is the distribution of multiple nodules scattered along the course of vessels. These nodules are inflammatory or aneurysmal. Occasionally they may be seen in the skin.

There is usually periarterial infiltration consisting for the most part of lymphocytes, polymorphonuclear leukocytes and often eosinophils. Fibrosis occurs in the adventitia and proliferation of the endothelium of the intima, which may result in occlusion of the vessel, in some

113. Horton, B. T.; Magath, T. B., and Brown, G. E.: Arteritis of the Temporal Vessels: A Previously Undescribed Form, Arch. Int. Med. **53**:400 (March) 1934.

114. Haining, R. B., and Kimball, T. S.: Polyarteritis Nodosa, Am. J. Path. **10**:349 (May) 1935.

115. Arkin, A.: Clinical and Pathological Study of Periarteritis Nodosa: Report of Five Cases One Histologically Healed, Am. J. Path. **6**:401, 1930.

116. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and Report of a Case, Ann. Int. Med. **7**:1345 (May) 1934.

instances by thrombosis. The media may show necrosis. This process gives rise to the aneurysmal dilatation and nodules on the walls of the vessels which characterize the disease. In some instances this feature may not be present.

In contrast to the findings in cases of thrombo-angiitis obliterans, the visceral arteries are essentially involved, while those of the periphery are involved uncommonly. According to Arkin,[115] the organs most frequently involved are the kidneys, heart, liver and gastro-intestinal tract; the muscles, peripheral nerves and central nervous system are less frequently involved. That the disease is capable of producing occlusion of the peripheral arteries is evident by the 3 cases reported by Barnard and Burbury,[117] in which gangrene of the fingers and toes occurred. In Carr's [118] case the onset was in the lower extremities with the rather early development of gangrene. Apparently this is exceptional.

Arkin [115] divides the disease into four stages: (1) the alterative degenerative or beginning stage, (2) the acute exudative inflammatory stage, (3) the stage of granulation or healing and (4) the stage of fibrotic scar tissue or end-stage.

The etiology is unknown.[116] The condition has been generally assumed to be of infectious origin, and the association with rheumatic fever [119] has been repeatedly noted. Friedberg and Gross [120] reported 4 cases in which the characteristic pathologic changes of periarteritis nodosa were present in addition to Aschoff bodies in the myocardium. In 1 of these cases there was also malignant nephrosclerosis. The disease occurred in 2 children following scarlet fever. There was no previous history of rheumatic disease. In 1 case in an adult there was a long-standing history of rheumatic fever, and in another only repeated attacks of tonsillitis and sore throat. The relation of this disease to allergy has also been suggested.[121] Mainzer and Joel [122] describe a typical case associated with sepsis lenta.

The clinical course is variable. It may be sudden in onset and violent and short in duration or insidious in onset, pursuing a subacute

117. Barnard, W. G., and Burbury, W. M.: Gangrene of Fingers and Toes in Case of Polyarteritis Nodosa, J. Path. & Bact. **39**:285 (Sept.) 1934.

118. Carr, J. G.: Periarteritis Nodosa, M. Clin. North America **13**:1121, 1930.

119. Neale, A. V., and Whitfield, A. G. W.: Rheumatism and Its Relation to Periarteritis Nodosa, Brit. M. J. **2**:104 (July 21) 1934.

120. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa: (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, Arch. Int. Med. **54**:170 (Aug.) 1934.

121. Masugi, M., and Sato, Y.: Periarteritis Nodosa Allergic Tissue Reactions in the Kidneys: Experimental Study on Pathogenesis, Tr. Soc. path. jap. **23**:857, 1933.

122. Mainzer, F., and Joel, W.: Periarteritis Nodosa als Ausdruck einer Sepsis Lenta (streptococcus viridans), Tr. Soc. path. jap. **23**:857, 1933.

prolonged course with variation in the presenting symptoms. These may be referable to only one organ or to one or more successively, thus reflecting the "hidden vascular insults." [114] The clinical manifestations are bizarre. Painful, tender muscles in association with cardiac, renal and abdominal symptoms may occur. Hematuria seems to occur in a majority of the cases at one time or another. The hemorrhage may be massive.[123] When the mesenteric vessels are involved there may be severe abdominal symptoms simulating an acute surgical emergency.[119] The continued fever with the picture of sepsis or infection associated with anemia and leukocytosis, sometimes with eosinophilia, seems to be fairly constant.

While the diagnosis [124] is seldom made ante mortem, the multiplicity of symptoms and findings may offer a suggestion, and if the possibility of this disease is kept in mind it would seem that the diagnosis should be more often correctly made. Certainly it seems to have been reported with increasing frequency in the past year or two.

RAYNAUD'S DISEASE

The conception of Raynaud's disease, originally described as a vasomotor neurosis, has been generally accepted until recently. Raynaud's description of the disorder stands, and clinically few important additions have been made in the description of its symptomatology and clinical course. Newer methods of investigation of vascular diseases have led to a better understanding of it and to more certain diagnosis. It must be admitted that errors in diagnosis have been and are frequent. This disease has often been mistaken for thrombo-angiitis obliterans because of the vasospastic phenomena frequently present.[125] Reactions to cold occasionally simulate the Raynaud paroxysm in this disorder. It has been described in cases of scleroderma, paroxysmal hemoglobinuria,[126] chronic arthritis,[127] tuberculosis [128] and other diseases. It would seem that this

123. Wever, G. K., and Perry, Isabella: Periarteritis Nodosa: Report of a Case with Fatal Perirenal Hemorrhage, J. A. M. A. **104**:1390 (April 20) 1935.

124. Grill, C.: Ein Beitrag zur Diagnose und Prognose der Periarteritis Nodosa, Acta med. Scandinav. (supp.) **59**:634, 1934.

125. (*a*) Allen, E. V., and Brown, G. E.: Raynaud's Disease: A Clinical Study of 147 Cases,, J. A. M. A. **99**:1472 (Oct. 29) 1923; (*b*) Raynaud's Disease: A Critical Review of the Minimal Requisites for Diagnosis, Am. J. M. Sc. **183**:187 (Feb.) 1932; (*c*) Raynaud's Disease Affecting Men, Ann. Int. Med. **5**:1387 (May) 1932. (*d*) Jäger.[69]

126. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation: A Variety of Raynaud's Disease, Heart **15**:7, 1929.

127. Allen and Brown (footnote 125 a, b, c).

128. Müller, G.: Conditions Resembling Raynaud's Disease in Patients with Tuberculosis of Both Hili: Two Cases, Wien. med. Wchnschr. **83**:1205 (Oct.) 1933.

disorder should be looked on as a syndrome occurring in a number of definite clinical entities as well as the typical idiopathic type.

Although a number of Maurice Raynaud's cases were in men, its predilection for younger women has been characteristic. Allen and Brown [125c] comment on the rarity of the disorder in men. They found 7 typical conclusive cases in men in a total of 150. There were 10 more in which the diagnosis was probable, making a total of 12 per cent. They state that functional vascular diseases affect men about as rarely as thrombo-angiitis obliterans affects women.

Bernheim and Garlock [129] believe that disturbances in calcium metabolism are factors in the development of Raynaud's disease and other vasospastic conditions. The reason for this is not entirely clear, but they think these phenomena develop in association with continued depletion of calcium and a negative calcium balance. Because of the unusual demand the parathyroid glands become hypertrophied, and continued hyperparathyroidism may result. In the earlier stages of the disorder adequate treatment with calcium in some cases resulted in considerable improvement. In others no benefit was obtainable. Six patients of this group, including some with Raynaud's disease and scleroderma, were subjected to parathyroidectomy. In 2 cases of uncomplicated Raynaud's disease astonishing improvement began immediately and has continued. In cases of scleroderma also considerable improvement has been noted. Assurance that a positive calcium balance continues postoperatively is necessary.

Lewis [126] has made many important observations. The reaction characteristic of Raynaud's disease occurs as a result of general or local exposure to cold. For the paroxysm to be produced by immersion of the hand in water, the temperature must be approximately 15 C. General exposure to room temperatures of from 13 to 18 C. was found to bring on the attack even when the patient was warmly clad and the hands were exposed.

Recovery in mild cases takes place quickly in a room temperature of 18.5 C. or more. The change in color from blue to red with a marked rise in temperature occurs rapidly as a result of relaxation of the affected vessels.

In more severe cases only partial recovery takes place at moderate room temperature, with partial temporary release of the spasm (intermittent leakage), resulting in arterial blood entering the cutaneous vessels and thus changing the color from blue to red. Little or no rise in surface temperature occurs. The color then returns to blue and fluctuates with the blood flow. At higher room temperatures the spasm is

129. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, Ann. Surg. **101**:1012 (April) 1935.

abolished. There is not necessarily a relation between color and temperature.

In severe cases there is persistent spasm at an ordinary room temperature, so that the temperature of the skin remains the same and the paroxysm is not relieved for long periods if the patient remains at rest. A high room temperature or increased physical activity is necessary to bring about relief. As a result of persistent spasms, blood flow is discontinued for a sufficiently long period to result in impairment of the integrity of the tissues, and dry gangrene of the tips may occur.

The normal reaction to overcooling, that is, by immersion in water at from 0 to 5 C., is reactive vasodilatation. In mild cases of Raynaud's disease the reaction is essentially normal. In the severer cases the reaction is modified by the tendency to vasoconstriction, especially at cooler room temperatures. The hand or fingers so treated become red but fail to show the typical rise in temperature of the normal extremity. The reaction is of the same type as that in the normal extremity, but is limited in extent and increased in duration, often being prolonged for several hours in a finger so exposed while in the other unexposed fingers spasm returns much earlier.

The site of the spasm in Raynaud's disease is in the digital arteries. No spasm exists in the veins; there is free passage of blood to the larger veins from the venules of the skin. The larger arteries of the hand are not usually affected.

Release of spasm occurs as the proximal parts to the spasm are warmed, resulting in the flow of warm blood to the vessels involved. Warming the distal portion does not release spasm.

In milder cases the arteries and arterioles of the fingers are intact, while in more severe cases complete dilatation does not occur but it is usually adequate.

Pallor and blanching of the skin appear in some attacks and indicate that the small vessels of the skin are empty. Cyanosis is more common. The circulation is shut off, but the small vessels in the skin contain blood from which oxygen is lost. In the presence of oxygenated blood the color is red. Blanching in some cases is infrequent and misinterpreted. Vasoconstrictor impulses to the minute vessels of the skin play no part.

According to these observations, paralysis of the vasoconstrictor nerves (by peripheral anesthesia) may not prevent spasm by exposure to cold, and spasm may be induced in susceptible vessels without nerve control.

When the vessels are in spasm and nerve block occurs with the release of normal vasoconstrictor tone, there is inhibition of normal vasoconstriction which allows warm blood to flow slowly into the fingers so that they become red without an increase in temperature. However,

at higher room temperatures this increase often is sufficient to tip the balance, and release occurs. Spasm is likewise more difficult to induce in nerve-blocked vessels because of the previous dilatation resulting from the release of normal tone and the consequent increased temperature.

The part played by the vasomotor nerves in the Raynaud syndrome when the spasm is induced by exposure to cold is definite, but it is not the primary cause. This consists of a local susceptibility in the vessels. The vasodilatation that follows nerve block is due to interruption of normal vasoconstrictor tone; some increased warmth results, and spasm is therefore less readily induced. In mild cases spasm under certain environmental conditions may be impossible, while even in severe cases the absence of normal vasoconstrictor tone may diminish the frequency of attacks.

This is further demonstrated, Lewis [126] says, by maintaining the hand in cold water with the temperature of the room fairly high. An abnormally high state of tone is induced in the vessels of the hand by immersion in cold water, but complete paroxysm does not occur until the room temperature is lowered. As a result of the additional increased vasoconstrictor tone which follows, complete spasm then results. The same degree of vasoconstrictor tone from low environmental temperature when the hand is at 30 C. is incapable of producing spasm. The vasomotor impulse excited reflexly by cold does not seem to be of unusual strength.

"It has been concluded from observation upon cooling of the fingers in cases of the type we have defined that an abnormality of the digital arteries exists; this displays itself in hypersensitivity of these vessels to relatively low temperatures."

The opposition to this conception of the pathogenesis of Raynaud's disease has arisen mainly from the observed effect of surgical interruption of the vasoconstrictor pathways with relief of the symptoms of the disorder in many cases by a number of workers.

Allen and Brown [125b] as a result of their unusually large experience have expressed the opinion that the disease is ordinarily an equivalent of psychoneurosis or neurasthenia.

Simpson, Brown and Adson [130] in the early stage of uncomplicated Raynaud's disease found no evidence that the digital arteries or arterioles were at fault, and they believe that the abnormality is wholly in the vasomotor nerves. Interruption of the sympathetic pathway in these cases results in complete relief of symptoms. In more severe cases

130. Simpson, S. L.; Brown, G. E., and Adson, A. W.: Observations on the Etiological Mechanism in Raynaud's Disease, Proc. Staff Meet., Mayo Clin. **5**:295, 1931; Raynaud's Disease: Evidence That It Is a Type of Vasomotor Neurosis, Arch. Neurol. & Psychiat. **26**:687 (Oct.) 1931.

the authors believe that the digital arterioles are secondarily involved and show evidence of increased susceptibility to cold, but primarily the causative factor is to be found in the vasomotor system, and the vessels show changes secondarily as the result of continued spasm. Adson [14] comments on the fact that climate seems to have very little effect. The disorder occurs in persons in very hot regions, and persons suffering from the affliction have not obtained relief by moving to warm climates. Adson cites the results of interruption of the sympathetic pathway by sympathectomy with complete relief from symptoms in many cases and almost universal relief in the lower extremities. This has been corroborated by many others. The more frequent failures in the upper extremities in his own cases and others he attributes to difficulties in operative technic and anatomic variations which have resulted in inability to sever all the sympathetic fibers.

This view is supported by the observations in 3 cases reported by Spurling, Jelsma and Rogers.[131] Extensive operations were carried out in 3 severe cases with relief of all the symptoms in the lower extremities, but with failure to secure permanent relief in the left upper extremity. The authors conclude that in certain cases of Raynaud's disease of the hands the condition is not curable or controllable by present-day operative measures on the sympathetic nervous system. They believe that the vasomotor system is primarily at fault and offer explanations similar to those of Adson. The authors state that the arterial pathologic changes which they observed are the result of recurrent continued angiospasm with involvement of the larger digital arteries more marked than that of the arterioles. These histologic observations consisted of thickening of the intima and media with hypertrophy of the smooth muscle fibers and separation of the layers by open spaces. There was complete obliteration of the small arteries proximal to the area of gangrene. The media of the arterioles contained hypertrophic smooth muscle cells.

Villaret and his associates [132] agree that the essential vascular disturbance in Raynaud's disease is arterial spasm. In proof of this they cite their experiments, which showed release of the paroxysm in Raynaud's disease following the injection of acetylcholine, which is an arterial dilator, and failure to obtain any improvement with histamine, which acts on the capillaries. The arterial spasm is the phase of white syncope of the paroxysmal crisis. With the reflex capillary dilatation

131. Spurling, R. G.; Jelsma, F., and Rogers, J. B.: Observations in Raynaud's Disease with Histopathological Studies, Surg., Gynec. & Obst. **54**:584, 1932.

132. Villaret, M.; Justin-Besançon, L.; Cachera, R., and Boucomont, R.: Etude critique sur la pathogénie des troubles circulatoires périphériques: Deuxiène syndrome de Raynaud, Arch. d. mal. du coeur **28**:1 (Jan.) 1935.

which follows the cyanotic asphyxial phase appears; this in turn disappears when the arterial spasm is released and arterial blood again enters the dilated capillaries, and the warm, red stage follows. In the asphyxial stage of the disease the appearance of the hand is almost identical with that in cases of acrocyanosis, but the essential differentiating factor, a low or normal venous pressure, in persons with Raynaud's disease is in contrast to the increased venous pressure of persons with acrocyanosis.

Villaret and his co-workers, in a review of the pathologic observations, strenuously oppose the view of Lewis that the fault lies in the local susceptibility of the vessels. While they admit that vascular lesions may be encountered, they say that these are usually reported to be in the smaller vessels of the skin while the essential localization of the spasm is in the digital arteries. Vascular changes are to be expected as a result of spasmodic crises repeated daily many times over a long period. Especially significant to them is the appearance of spasm of the blood vessels as a result of injury or irritation to the vasomotor nerves. The authors are convinced that the paroxysms of Raynaud's syndrome are entirely mediated by the sympathetic nervous system.

While it appears that the two views are not reconcilable, this may not be true. There are certain facts which lead one to believe that the fault may lie in any part of the neurovascular mechanism and that it is not always the same in all cases. The Raynaud syndrome, occurring atypically, it is true, in cases of thrombo-angiitis obliterans must be due to a local increase in vascular susceptibility to cold. In the case reported by Gagel and Watts [133] the typical syndrome developed in a patient with carcinomatous metastasis to the spinal cord. The response of typical Raynaud paroxysms in moderately severe cases to stimuli of emotion and pain, even at a relatively high environmental temperature, is so well known that comment is not needed. However, it is equally possible that the end-result is an exaggerated vascular response to a normal stimulus as that it is an excessive stimulus to a normal vessel which results in exaggerated vascular reaction.

Graham [97] suggests that, whether the original causative factor is a local vascular fault or of neurogenic origin, spasm of the small arteries occurs and structural changes in these vessels are responsible for the nutritional changes in the tissues characteristic of the severer forms of the disorder. Repeated minimal trauma, not sufficient to cause impairment in normal vessels, may be responsible for thrombosis of the small arteries and capillaries. This may end in defects in the tissue and may account for the local vascular fault, secondary rather than primary.

133. Gagel, A., and Watts, J. W.: Zur Pathogenese der Raynaudschen Gangrän. Ztschr. f. klin. Med. **122**:110, 1932.

Morton and Scott [134] present an excellent conception. They comment on the induction of attacks by exposure to the proper degree of cold as well as by reflex painful and psychic stimuli when environmental conditions are suitable. In some cases they have noted that psychic stimuli are more potent than exposure in the induction of a paroxysm, at least in regard to frequency.

In the main, Morton and Scott confirm the conclusions of Lewis and Landis [135] as to the degree of temperature necessary to produce the paroxysm, the progress of the attack and the changes of color which follow release of the spasm, as well as other reactions to temperature. They state: "It seems certain from these studies that the essential abnormality in Raynaud's disease is a local hypersensitiveness of the peripheral smaller arteries to cold, as Lewis has emphasized." They believe that the vasoconstrictor influence should be emphasized because it does play an important rôle, as shown by the initiation or accentuation of paroxysms by psychic and nervous influences. While Raynaud's disease is not primarily due to an abnormality of sympathetic innervation, the majority of attacks are initiated or accentuated by vasoconstrictor influences under the ordinary living conditions of these patients. Regional anesthesia always causes improvement in the circulation to an ischemic extremity, though in the more severe cases the most distal part might remain uninfluenced by it.

In fact, Morton and Scott express the opinion that a dual mechanism must be responsible for these spasms in the peripheral vessels: first, essentially a hypersensitiveness to cold and, second, vasoconstrictor influences of normal type, which are important in bringing on and maintaining attacks. Therefore, their removal may be effective in the prevention of the paroxysms or in the reduction of their frequency.

Allen and Brown [127] state what they regard as the necessary criteria for diagnosis. These are: (1) intermittent attacks of discoloration of the acral parts, (2) symmetrical bilateral involvement, (3) absence of clinical evidence of occlusive lesions of the peripheral arteries, (4) gangrene or trophic changes limited in a large degree to the skin, (5) two years as the minimal period of duration, (6) absence of organic disease to which the vasomotor changes might be secondary and (7) predilection of the disease for females.

SECONDARY VASCULAR SPASMS

In addition to the typical Raynaud syndrome several writers have described secondary vascular spasms of a more or less localized type,

134. Morton, J. J., and Scott, W. J. M.: Some Angiospastic Syndromes in the Extremities, Ann. Surg. **94**:839 (Nov.) 1931.

135. Lewis and Landis.[48] Lewis.[126]

which are often more persistent in their action than paroxysmal. There may be an exaggerated type of response to cold.

Morton and Scott [134] list the nervous diseases in which they have noted angiospasm of the peripheral vessels. Among these are anterior poliomyelitis, hemiplegia in the later stages, spina bifida and amyotropic lateral sclerosis. Angiospasm may also be consecutive to trauma of many different types, fractures, sprains and contusions, as well as to causalgia when the main nerve trunks are implicated. Hypersensitivity to cold is outstanding in cases of angiospasm of this type; it may continue long after the acute effects of the trauma have subsided. This tendency to spasm may then pass into a latent stage, only to recur when exposure to the proper degree of cold occurs. De Takáts and Mackenzie [26] point out syringomyelia, multiple sclerosis and other diseases of the central nervous system, as well as lesions of the peripheral nerves, neuritis, perineuritis and cervical rib, as possible causes.

In cases of cervical rib the symptoms are usually motor and sensory and less frequently vascular. Telford and Stopford [136] have described the symptoms in 3 typical cases. The arm most used was involved, and the index finger was the first to show gangrene. The sequence of events was initial pallor, coldness, numbness and gangrene. There was a cessation of all pulse below the junction of the axillary and brachial arteries. The occlusion was limited to those vessels receiving their vasomotor nerves from the somatic nerves and did not occur in the subclavian and axillary vessels, which receive their nerve supply from the perivascular plexuses extending into the arm.

There is considerable variation in the anatomic distribution of the sympathetic fibers, and it is only when these emerge in the lowest branch of the plexus in contact with the cervical rib that symptoms of a vascular nature develop as a result of irritation of the fibers. The anatomic changes in the vessels are explained by long continued spasm of the muscular coat with resultant interference with their blood supply by compression of the vasa vasorum and the development of pathologic processes in the walls of the vessel which predisposes to thrombosis. The thrombosis begins in the smaller vessels of the fingers and extends upward into the larger vessels.

Symptomatic recovery takes place following surgical removal of the cervical rib.

In another case [137] the reaction to immersion in cold water was blanching pallor, while the other hand was normal. The radial and ulnar

136. Telford, E. D., and Stopford, J. S. B.: Vascular Complications of Cervical Rib, Brit. J. Surg. **18**:557, 1931.

137. Blair, D. M.; Davies, F., and McKissack, W.: The Etiology of the Vascular Symptoms of Cervical Rib, Brit. J. Surg. **22**:406 (Jan.) 1935.

arteries were not palpable, but there was marked pulsation in the axillary artery, so that aneurysm was suspected. After operation this disappeared and pulsations returned in the other arteries. At autopsy a few days later, marked endoneural thickening and proliferation were noted in the first dorsal nerve and the inferior part of the lower trunk of the plexus where it was related to the cervical rib. This lesion was thought to be responsible for the irritation of the sympathetic fibers producing the widespread vasoconstriction.

DISEASE OF PERSONS USING THE PNEUMATIC HAMMER

The reports of cases of vasospastic disorder in the hands of persons operating the pneumatic hammer used by limestone cutters have served to redirect attention to this peculiar abnormality, which occurs particularly among limestone workers.[138] The hammer used is driven by air pressure and has a vibration frequency of from 3,000 to 5,000 a minute. The symptoms are blanching and numbness of the fingers which guide the instrument, particularly the fourth and fifth.

After about a year of manipulation of the hammer the attacks of "dead finger" begin to appear, usually on exposure to cold, especially in the morning or after work with the hammer is discontinued, almost never while the hammer is in operation. Even after years during which pneumatic tools have not been used the attacks may come on in the affected fingers when exposed to cold. Relief from the attack is afforded by rubbing or other methods of warming and, it is said, by operating the tool.

No serious phenomena follow; gangrene or impairment of tissue integrity do not occur. Most stonecutters who have the disorder pay little attention to it and consider it part of their occupation.

ERYTHROMELALGIA

Brown [139] considers this the most typical example of a primary vasodilatation disturbance. He considers it a disease entity which is often confused with the phenomena which occur in cases of polycythaemia vera, thrombo-angiitis obliterans, gout, low grade forms of cellulitis, peripheral neuritis or the overactive stage of Raynaud's disease, poisoning by arsenic and thallium and even arteriosclerosis. This confusion is

138. Hardgrove, M. A. F., and Barker, N. W.: Pneumatic Hammer Disease: A Vasospastic Disturbance of the Hands of Stone Cutters, Proc. Staff Meet., Mayo Clin. **8**:345 (June 7) 1933. de Takáts and Mackenzie.[26a]

139. Brown, G. E.: Vasodilation Disturbances Affecting the Extremities: A Clinical Study, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 241; Erythromelalgia and Other Related Disturbances in the Extremities Accompanied by Burning Pain, Am. J. M. Sc. **183**:468, 1932.

due to a misconception as to what constitutes erythromelalgia, and the term has been loosely applied to the syndrome of any red painful extremity with paresthesia.

True erythromelalgia is characterized by the following features:

1. Bilateral burning pain in the extremities, often occurring intermittently in attacks.

2. A sharp increase in the local temperature of the affected part, with redness, flushing and congestion varying in degree.

3. Production and aggravation of the distress by heat and exercise.

4. Relief by rest, cold and elevation.

The patient has attacks of vasodilatation, with huge increases in the flow of blood in the extremities affecting both the superficial and the deep vessels. Redness may or may not be a prominent feature, depending on whether or not the superficial vessels of the skin participate in the vasodilatation. That the larger vessels are involved seems to be indicated by the marked increase in the oscillometer readings during the attack.

The etiology is not known, but Brown believes that it is the result of some disturbance in the vasomotor centers which accounts for the bilateral distribution of the disease. In 10 of 85 cases of burning pain of the hands or feet the symptoms were found to fill the requirements for the diagnosis of erythromelalgia. There were 3 cases in which the phenomena were typical except that they occurred unilaterally.

In these cases, with the induction of an attack with exercise, heat or posture, the surface temperature would increase to 35 or 36 C. Pain would begin at about 33 C.; flushing of the skin usually accompanied this rise and often pulsation in the larger veins, hyperhidrosis and paresthesia. In 1 case a refractory period without symptoms of from seven to ten days followed severe attacks.

Calorimetric determinations of loss of heat in an affected foot in this case showed a change from 33 small calories per minute for the entire foot when normal to 205 calories per minute during an attack. This, Brown estimates, indicates an increase of more than 600 per cent in the flow of blood during the period of vasodilatation. The oxygen content of the venous blood of this foot showed a value of 57 per cent when normal, and during an attack this rose to an oxygen saturation point of 83 per cent, approaching that of arterial blood.

In another group of patients with degenerative vascular disease involving the central nervous system there were paresthetic sensations of heat and burning pain, numbness and tingling, often unilateral. However, the patients in this group failed to fulfil the requirements for the diagnosis of erythromelalgia, not showing the correlation of temperature with symptoms and, if they did, showing the onset of symptoms at

from 31 to 32 C. The patients failed also to show relief with a decrease in surface temperature.

The phenomena of vasodilatation which occur in cases of polycythaemia vera are emphasized by Brown, who states that in half the cases there was this major complaint of burning pain in the hands or feet due to a true vasodilator disturbance with increased heat production, elevated temperatures of the parts and marked redness during the painful periods. The change was often unilateral. When the disease was controlled by treatment with phenylhydrazine the symptoms disappeared and attacks could not be induced. Bleeding also sometimes gave dramatic relief from the symptoms. There was a rough parallelism between the volume of blood and the output of heat in an affected part.

Polycythaemia vera should be considered in every case in which burning pain in the extremities is a major symptom.

In direct contrast to this point of view is that of Lewis,[140] expressed in the report of his studies on burning pain. He is of the opinion that "so-called erythromelalgia" is not a disease entity, that it is a symptom complex seen in many disorders and is not necessarily associated with vasodilator phenomena but may be. He proposes the term erythralgia to denote the burning redness which he found to be of identical type in cases of dermatitis factitia, erythrocyanosis, chilblain, thrombo-angiitis obliterans, senile arteritis and so-called erythromelalgia. He believes this to be identical with that of chronic inflammatory states of the skin and of the skin injured by ultraviolet rays, freezing, burning, scratching and the like.

He found the reaction producing the characteristic symptoms to be the same regardless of the method by which it was produced. Particularly likely to set off the pain-producing mechanism was any method by which the temperature of the hands or feet might be increased beyond a certain critical point, which was somewhat variable in cases of different type but in 1 case was of the same degree as that which Brown found in his typical cases.

When the temperature was raised by immersing the feet or the hands in warm water the symptoms developed at nearly the same level in all succeeding experiments. The same thing happened when the extremities became warm as a result of warming of the body or when the temperature of the feet and hands was increased by exercise, such as walking. Friction had the same effect. The pain usually occurred as a result of an increase in temperature but would sometimes appear without such an increase. The conclusion was reached that, though vasodilatation

140. Lewis, T.: Clinical Observations and Experiments Relating to Burning Pain in the Extremities and So-Called Erythromelalgia in Particular, Clin. Sc. **1**:175 (Dec.) 1933.

may be present with pain, it is not a necessary part of the mechanism. It is also pointed out that a rosy color alone is not evidence of vasodilatation without an increase in temperature and that vasodilatation does not occur when the affected extremity is dependent. Further, many other parts of the skin may show this reaction; it may be unilateral as well as bilateral, and the skin of the trunk is often involved. Urticaria factitia is a frequent accompaniment. Obstruction to the venous circulation was also an effective means of inducing the pain reaction, which subsided in a few minutes after release.

The explanation offered is that the skin in all these cases is in a "susceptible state;" that is, the condition giving rise to these symptoms is located in the skin itself. This susceptible state is the result of some injury or inflammation, perhaps chronic or residual, by which the capillaries and small vessels are reduced to a toneless condition which results in the reddening of the skin when the part is dependent and is due to passive congestion and not to vasodilatation.

The stimuli capable of producing pain in persons whose skin is in the susceptible state are: (1) increase in the temperature of the skin to a certain level normally insufficient to produce pain either by increased blood flow or application of heat from without, (2) extreme cold, (3) local friction and (4) tension when it comes with walking, caused by warming of the foot both by increased blood supply and by friction. When pain occurs in a limb allowed to hang down it is due to hydrostatic vascular tension.

Burning pain has for its underlying basis the release from damaged tissues of a natural substance which acts on the pain nerve endings and lowers the threshold of these to tension and heat, causing them to discharge pain impulses even at a moderate increase of temperature or tension from dependence of the limb.

Severe burning pain of the fingers in cases of Raynaud's disease can be caused by quick warming of the fingers occasioned by a return of blood to them when they are cold. The same phenomena are present in normal fingers if the range of temperature is sufficiently increased.

It seems that Brown has answered one of Lewis' important questions, which he says has not been satisfactorily answered: "Is the vasodilatation which may accompany pain an abnormal one?" Lewis says that no evidence has been presented to show that it is abnormal for the circumstances in which it occurs. However, in the case described by Brown [139] there were both an extraordinary increase in the blood flow during the attack and an increase in the oxygen tension of the venous blood to 83 per cent. These findings would surely indicate an associated abnormal vasodilatation.

Brown [139] also recognizes such conditions as Lewis describes. These he considers as burning paresthesias and sharply differentiates them from

erythromelalgia by the absence of evidence of marked vasodilatation, as indicated by high surface temperatures. He considers a surface temperature during attacks of 33 or 34 C. or more to be a requirement for diagnosis in addition to the other criteria which have been mentioned.

ACROCYANOSIS

This is a poorly understood condition which probably represents a secondary symptom complex, although a primary permanent form has been described.[141] There is some confusion as to the mechanism of the local vascular disturbance, and the diagnosis is often mistaken. The syndrome is frequently seen but sometimes overlooked because of the few subjective symptoms and because there are no serious consequences.

Lewis and Landis,[142] with their report of observations on a case of acrocyanosis, briefly reviewed some of the earlier reports with descriptions of the disorder. Boettiger [143] describes the condition occurring in patients with acromegaly. Layani [144] describes the condition mainly in women. The hands are a persistent blue-red from a little above the wrists, and the color increases somewhat in intensity distally. The skin is cold, and the palms sweat rather profusely. The condition of the skin is otherwise normal. Puffy swelling of the fingers and hand is sometimes seen. Parrisius [145] saw the venous limbs of the capillaries to be distended, as well as the venules of the subpapillary plexus. He could not see a flow of blood in the capillaries.

Observations on their case led Lewis and Landis to believe that the essential vascular defect in this condition is the result of increased tone of the arterioles of the skin of the hands at ordinary environmental temperatures. Because of this, the inflow of the blood to the capillaries is diminished, oxygen is released and the superficial vessels, both capillaries and venules, are filled with blood which has lost oxygen. These investigators found the hands constantly cold and cyanotic, which they felt was due to stasis in the small vessels. Observations on the capillaries confirmed this.

Likewise, they were able to demonstrate that the defect was arterial and spasmodic, since the vessels were capable of normal dilatation if

141. Villaret, M.; Justin-Besançon, L. Cachera, R., and Boucomont, R.: Etude critique sur la pathogénie des troubles circulatoires périphériques: Les acrocyanoses, Arch. d. mal. du coeur **27**:725 (Dec.) 1934.

142. Lewis, T., and Landis, E. M.: Observations upon the Vascular Mechanism in Acrocyanosis, Heart **15**:229, 1930.

143. Boettiger: München. med. Wchschr. **46**:1733, 1899; quoted by Lewis and Landis.[142]

144. Layani, F.: Les acrocyanoses, Paris, Masson & Cie, 1929.

145. Parrisius: Deutsche Ztschr. f. Nervenh. **72**:310, 1921; quoted by Lewis and Landis.[142]

the increased tone was released by increased environmental temperature. In contrast to the findings in persons with Raynaud's syndrome, histamine caused release of the spasm, resulting in an increased surface temperature which fixed the location of the obstruction in the arterioles.

Direct observations of the pressure in the venous capillary limbs gave results essentially the same as those noted in normal persons with a normal rise and fall after the obstruction and release of the venous return flow of blood. Lewis and Landis therefore concluded that the venous portion of the circulation is not responsible.

That vasomotor increase in tone is not responsible but that the cause is in the arterioles themselves is also concluded. Anesthetization of the ulnar nerve brings a late change only in color but a normal increase in temperature. The delay is interpreted as indicating that the deeper anastomotic vessels of the fingers open, allowing an increased flow of blood to warm the finger. The arterioles then respond to the warmth by a release of tone. The color reaction can be returned to the cyanotic tone when the vasomotor pathway is blocked, by immersion of the hand in water at 17 C.

The only explanation offered by Lewis and Landis as to the actual etiology is that the phenomenon is the result of impairment of the function of the superficial vessels of the skin as a result of exposure to cold, since only the exposed portions of the hands seem to be affected.

Villaret and his associates [141] present a different conception of this condition. According to their view, capillary and venous dilatation constitutes the essential physiopathologic characteristic of acrocyanosis. They found a uniform increase in venous pressure in all cases. They believe the underlying causes of the vascular phenomena to be either on an organic basis, particularly with involvement of the vasomotor center and the vasomotor nerves, or on an endocrine basis. Among the causes of the former type they include syringomyelia, tabes and myelitis and particularly stress the association with sequelae of encephalitis. Alterations in the peripheral nerves with various types of neuritis are not uncommon in acrocyanosis. On the other hand, the disturbance in the sympathetic nervous system which results in this peculiar vascular condition may be entirely functional, and this is most often the case, according to the authors.

With this vascular disorder there is often noted an endocrine disturbance—ovarian, thyroid and adrenal. The condition may appear in both sexes about the time of puberty. The authors are inclined to believe that some pituitary functional disorder is the background for this rather indeterminate condition and conclude that basically there is a glandular-sympathetic coupling in the etiology of acrocyanosis, which they prefer to designate a humeroneurosis.

As proof of their contention that the fault lies in the capillary venous side of the circulation, the authors offer the observations on venous pressure, the values for which they have found to be always elevated in cases of acrocyanosis, in contrast to the observations in cases of Raynaud's disease, in which the values are depressed during the spasm, rising again afterward. The authors consider observations of venous pressure to be a most important measure in the study of vascular disorders and believe that venous pressure is the only available yardstick of the phenomena of the capillary venous circulation.

Landis and Gibbon [43] found that by immersion of the opposite extremities in warm water the temperature of the affected extremities failed to rise as it does in normal persons. Nerve block, however, brought about a rise in temperature to the normal level of vasodilatation, and the color eventually returned to normal. The parts involved always returned to normal color when warmed. When histamine was pricked into the skin the region of the flare became red in sharp contrast to the cyanotic color of the surrounding skin. These observations also speak for arteriolar spasm as the principal mechanism in the condition.

Brown [139] has frequently seen the disorder in asthenic adolescent boys and girls or following chronic diseases, such as arthritis. He says that this condition, like other similar functional disorders, represents an exaggeration of the normal response of vessels of the surface to cold or psychic stimulation in that the thresholds of stimulation in the centers of the cord and brain are modified by disease, growth or glandular disturbances.

THROMBOSIS INDUCED BY EFFORT

This condition has been reported with increasing frequency.[146] It seems probable that the relationship of effort to thrombosis may be frequently overlooked and the condition considered thrombophlebitis. Matas,[146a] in an excellent review of the literature, has given a clear description which should aid greatly in its recognition.

It is his opinion that trauma in some form, trivial or violent, is the essential cause of the pathologic process in the vast majority of cases. Injury to the vein may be brought about by stretching or by contusion. In the case of thrombosis of the axillary vein, which is the vessel most often involved, compression between the clavicle and the first rib may be important. Gout, chronic plumbism, the rheumatic state and a variety of infections may be predisposing factors, but in some cases no such condition can be found. In the majority of cases the clinical course

146. (*a*) Matas, R.: On So-Called Primary Thrombosis of the Axillary Vein Caused by Strain, Am. J. Surg. **24**:642, 1934. (*b*) Ballon, H. C.: Primary Thrombosis of the Axillary Vein, Canad. M. A. J. **31**:414 (April) 1935.

and cultures of the thrombus and blood fail to show evidence of infection.

Venospasm has been described. That obstruction of the lumen of the vein is not the sole cause of the impairment to venous return is indicated by the extraordinarily rapid development of edema in some cases. It seems as though irritation of the perivenous plexuses in the wall must be the cause of extensive venospasm. Several cases have been reported in which operation failed to reveal thrombosis or any actual occlusion; the vein was found to be in a state of rigid spasm, thus causing obstruction to the circulation. Thrombectomy was carried out and the damaged section of the vein removed. Vasomotor equilibrium was restored, and the consequent edema quickly disappeared.

The clinical features are characteristic. Marked edematous swelling of the arm appears immediately or, less often, at a varying interval after strain or repeated or long-continued muscular effort. The edema spreads rapidly over the whole arm without associated fever. There is no local inflammation or constitutional reaction. The skin may be livid or cyanotic. Collateral venous channels may be visible on the shoulder and the wall of the upper part of the chest. A palpable tender cord may be found in the axilla corresponding to the axillary vein. Hematologic studies in those cases in which they were carried out did not reveal any characteristic deviation from the normal. The frequency of relapse when the same type of occupation or effort is persisted in is characteristic. Horton,[147] in his carefully studied case, noted diminished oxygen saturation of the venous blood in the affected arm but no deviation from the normal in regard to findings in the blood. He states that polycythaemia vera must always be considered.

In regard to treatment, Matas concludes that in all cases in which the usual methods of treatment for thrombophlebitis are not effective an exploratory operation is indicated to uncover the nature of the lesion; thrombectomy should be performed if a clot exists or excision of the venous section involved, whether a clot is found or not.

LATENT PHLEBITIS

While no attempt is being made to cover the subject of thrombophlebitis, so-called latent phlebitis is probably of sufficient importance to be mentioned briefly. Whether or not thrombosis may occur without inflammation, it is likely that intravascular clotting may take place in veins as a result of certain alterations of the blood.[148] Injuries, chemi-

147. Horton, B. T.: Primary Thrombosis of the Axillary Gland, J. A. M. A. **96**:2194 (June 27) 1931.

148. Shevkunenko, V. N.: Anatomic Types of Veins and Experimental Thrombophlebitis, Sovet. khir. **5**:50, 1933; abstr., J. A. M. A. **102**:1348 (April 21) 1934. Nordmann, M.: Kreislaufstörungen und pathologische Histologie, in Kisch, B.: Ergebnisse der Kreislaufforschung, Dresden, Theodor Steinkopff, 1933, vol. 4. Nygaard and Brown.[88]

cal or traumatic, as well as inflammatory reactions, are the principal causes. That infection may remain latent and activation of ancient infections may occur under suitable conditions has been emphasized by de Takáts [149] in a discussion of resting infection in varicose veins.

He mentions a group of cases in which infection had subsided to a point where there were no clinical signs, only to suffer activation later. He believes the source to be primarily infected teeth and tonsils, pelvic infections, varicose ulcers and acute infection of the respiratory tract, and mentions low grade infection of the adjacent tissue as well. Trauma, injections into the veins or an operation may induce an acute episode.

Schmidt [150] and Meyer [151] have recently drawn attention to the importance of this condition. It is bacterial in origin, according to Meyer, and may be acute or chronic. It usually develops in a vein at the site of some previous inflammation, which may or may not have been evident. The patient is usually unaware of the condition and his complaints usually suggest rheumatic involvement. The condition is said to be exceedingly common. Foci of infection as well as injuries, Meyer also considered the usual sources.

Easy fatigue and cramplike pains in the legs, which are more often present at night, are sometimes complained of. "Barometric sensations" with aching pain accompanying changes of the weather are emphasized. Slight edema may occur at night, and local eczema or itching is an important sign. Pain is the cardinal symptom, and the deep veins of the lower part of the leg are sensitive to pressure. Observation has shown that tenderness can usually be elicited at points where the deeper veins of the foot and leg can be pressed on.

The condition can easily be confused with thrombo-angiitis obliterans, but an intact arterial circulation serves to differentiate it. Myalgias may cause confusion. Chronic arthritis is seldom associated with phlebitis, but with a mild acute condition in the joints the contrary is true, according to Meyer, who insists that such latent infections frequently furnish a focus of infection in cases of acute arthritis which is usually overlooked. With activation of such an infection acute deep thrombophlebitis may develop, with the usual picture of edema, fever, local pain and the like.

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149. de Takáts, Géza: "Resting Infection" in Varicose Veins: Its Diagnosis and Treatment, Am. J. M. Sc. **184**:57 (July) 1932.

150. Schmidt, C. L.: Zur Diagnose der latenten Phlebitis in den unteren Extremitäten, München. med. Wchnschr. **82**:290 (Feb. 2) 1932.

151. Meyer, O.: Das Krankheitsbild der latenten Phlebitis, Deutsche med. Wchnschr. **61**:595 (April 12) 1935.

TREATMENT

No attempt can be made to consider all the numerous therapeutic measures applied in cases of peripheral vascular diseases. Some have rather general application; others are limited to particular purposes. Sometimes therapy can be directed etiologically. This is particularly true in the secondary types of vascular disease, for example, in those developing in the course of polycythemia vera, hypothyroidism and specific infectious diseases like syphilis or even rheumatic fever. Diabetic vascular disease must be treated from the point of view of diabetes as well as that of the blood vessels.

That associated cardiac disease, especially in cases of disturbances in mechanism, such as auricular fibrillation and decompensation,[153] which occur frequently in association with arteriosclerosis obliterans, must receive adequate attention is axiomatic.

The treatment of both acute and chronic foci of infection has been emphasized by many, and the importance of general management of the patient has been universally recognized. Careful attention to detail often marks the difference between success and failure.

As an important principle in the treatment of this group of disorders Reid [22] states that every possible effort should be made to save an affected arm or leg during a critical period, because a circulatory balance will often eventually be established, and in the milder types or early stages of the disease many persons can be spared the development of gangrene by the application of simple therapeutic measures. This expresses the general conservative view which most of the workers in this field have mentioned. As a result of the application of proper measures, major amputations are necessary much less frequently than they were even a few years ago.[75]

Many of the general principles of treatment are applicable to all types of organic occlusive disease. The age of the patient, the general condition and the type of pathologic process may bring into consideration special types of management. The care of the feet when circulation is only mildly impaired is as important as when impairment of the integrity of the tissue exists, regardless of the cause. The necessity of keeping them warm and dry and free from even such minor infections as might result from small abrasions and the avoidance of minor contusions have been emphasized repeatedly. Not only is it important to keep the extremities themselves protected from cold by the use of proper shoes and clothing, but the whole body must be kept warm because of the important rôle of the extremities in the conser-

152. Footnote deleted.

153. Samuels, S. S., and Feinberg, S. C.: The Heart in Thrombo-Angiitis Obliterans, Am. Heart J. **6**:255 (Dec.) 1930. Footnote 26.

vation of body heat by means of the vasoconstrictor mechanism.[154] This is an important measure in cases of Raynaud's syndrome as well as in those of obliterative disease.

Rest, by which is meant rest in bed with the extremities in a horizontal position, has been particularly widely emphasized as of the utmost importance in all types of obstructive vascular disease.[155] Not only is this important, but it is necessary to find the level of greatest circulatory efficiency, which is usually from 10 to 15 degrees below the horizontal. Postural exercises[156] and contrast baths[31a] are aids in increasing the circulation, particularly in the absence of gangrene. The use of the heat-cradle and baking appliances have long been advised.[31a]

It has been found that the degree of heat applied is of importance, particularly in cases in the advanced stage, when gangrene or ulceration is present. Pain is often intensified by too high a temperature. Starr[157] found that the optimum temperature for the relief of pain is from 33 to 35 C. Temperatures higher than this increase the metabolism of the tissue, and thus a greater supply of oxygen is needed. The increase in circulation which would normally follow the increase in temperature fails because of the vascular disease, and circulation becomes inadequate.

To overcome these difficulties Starr devised a constant temperature foot-cradle by means of which the environmental temperature could be controlled exactly. In addition, oxygen could be supplied locally and arrangements for desiccation introduced within the chamber. The usefulness of the oxygen was questionable, but no doubt existed as to the value of the controlled temperature, and desiccation was useful, particularly in the presence of gangrene. The experience of Severinghaus[158] with a constant temperature foot-cradle without oxygen or desiccation has been similar and leaves no doubt as to the value of proper control of temperature.

The relationship of tobacco to vascular disease has been discussed with thrombo-angiitis obliterans. The evidence is so conclusive that no doubt can be felt as to the rôle which tobacco plays in producing peripheral vasoconstriction, even though the question of its exact rela-

154. Coller and Maddock.[16] Maddock and Coller.[21]

155. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans, J. A. M. A. **102**:436 (Feb. 10) 1934. Brown, Allen and Mahorner.[25] Samuels.[30]

156. Allen, A. W.: Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, Ann. Surg. **92**:931, 1930. Buerger.[23]

157. Starr, I., Jr.: On the Use of Heat Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Diseases, Am. J. M. Sc. **187**:489 (April) 1934.

158. Severinghaus, E. L.: A Constant Temperature Foot Cradle, Am. J. M. Sc. **187**:509 (April) 1934.

tion to etiology is not settled. The observations previously discussed have again been corroborated by Lampson,[159] using both the temperature tests and the plethysmographic methods of measurement. He concludes, as have most previous workers, that smoking and inhaling cigaret smoke cause sudden marked peripheral vasoconstriction and that smoking is contraindicated in persons having peripheral vascular disease. This applies not only to persons with thrombo-angiitis obliterans, with which tobacco is usually associated, but to persons with any other types of circulatory impairment.

Induction of artificial fever by the intravenous injection of typhoid vaccine was popularized by Brown and his associates.[25] It is a widely used and useful form of therapy, the principal application of which in peripheral vascular diseases is in thrombo-angiitis obliterans. That general peripheral vasodilatation occurs during, and follows for several hours after, the fever is unquestioned. Its principal drawbacks are the initial chill with the attendant period of vasoconstriction, during which thrombosis has rarely occurred, the discomfort to the patient and the danger attendant to its use in older persons with degenerative cardiovascular or renal disease.[31a] Brown has recommended the use of a special type of vaccine with which the chill is diminished.

De Takáts is of the opinion that chill and high fever are unessential and suggests that minimal doses of typhoid vaccine be employed. With these subreactional doses vasodilatation can be produced without fever or discomfort and with complete safety. The dose employed is from 100,000 to 1,000,000 bacteria. The dose must be cautiously increased when vasodilatation fails to occur.

This suggests, as does the experience of Maddock and Coller,[154] that other methods of producing vasodilatation by heat might be equally effective. Reid [22] has also suggested the careful administration of thyroid extract, by which the metabolic rate might be increased. Keeping the patient in an environment of relatively high temperature has been suggested, by the use of the heat cabinet of Lewis [12] or the insulated blanket of Maddock and Coller [154] or by the application of other methods of raising the body temperature. Heat has also been applied by means of diathermy locally with definite improvement.[160]

Intravenous injections of saline solution have been applied mainly in the treatment of thrombo-angiitis obliterans. Samuels [161] briefly traced

159. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, J. A. M. A. **104**:1963 (June 1) 1935.

160. Perlow, S., and Blakely, Katherine: Local Diathermy in Peripheral Vascular Disturbances, J. A. M. A. **101**:1869 (Dec. 9) 1933.

161. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans: Further Experiences with Treatment, J. A. M. A. **102**:436 (Feb. 10) 1934.

the use of various types and strengths of solutions, until Silbert [162] recommended the use of a 5 per cent solution of sodium chloride. Solutions of lower concentrations are sometimes employed (from 2 to 3 per cent), especially in older patients. Samuels [161] finds that after the injection of the hypertonic solution there is a consistent increase in the pulse amplitude and pulse pressure shown by the oscillometer. This method is not specific for thrombo-angiitis obliterans, but it is to be considered as a "mechanical aid in the enhancement of collateral circulation in the extremities." Improvement is said to be prompt, especially in milder cases. In the more severe cases 300 cc. of the solution is given intravenously daily until the gangrene or ulceration is healed.

Extracts of tissue have been introduced into the treatment of peripheral vascular diseases rather recently. Barker, Brown and Roth [163] have been able to confirm the work of their predecessors, which they briefly review, that intermittent claudication can be relieved by treatment with several extracts of tissue. They employed an insulin-free pancreatic extract, an extract of skeletal muscle, muscle adenosin phosphoric acid and adenosin. These substances were all given intramuscularly, and, in addition, the extract of skeletal muscle was given orally.

There was an increase in the time necessary to produce claudication, that is, a greater amount of exercise could be performed before the development of pain, with all the preparations. The best results were obtained with the insulin-free pancreatic extract, after the administration of which 92 per cent of 55 patients with thrombo-angiitis obliterans and arteriosclerosis obliterans showed an increase in the time necessary to produce claudication with the standard walking test employed. Similar results were obtained with the other preparations, but all the extracts proved somewhat less effective in the cases of arteriosclerosis than in those of thrombo-angiitis obliterans.

The composition of the extracts is not known. They had little or no effect on pain while the patient was at rest or on the pain of gangrene. It was impossible to demonstrate that the relief of claudication was due to vasodilatation, since there was no significant rise in surface temperature and the relief of pain was more marked than that afforded by drugs or other methods of producing vasodilatation. In this Barker and his associates are not in agreement with previous investigators. It would seem that the effect obtained is that of an increased ability of the muscle to work with the available blood supply. Many patients

162. Silbert, S.: The Treatment of Thrombo-Angiitis Obliterans by Intravenous Injection of Hypertonic Salt Solution, J. A. M. A. **86**:1759 (June 5) 1926.

163. Barker, M. W.; Brown, G. E., and Roth, Grace M.: Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), Am. J. M. Sc. **189**:36 (Jan.) 1935.

seemed to do well with one injection a week. The therapeutic value of the extracts of tissues seemed to be restricted to those cases in which intermittent claudication was the main symptom.

Drugs which are of value in the treatment of peripheral vascular disease are few and somewhat limited in usefulness except those affording relief of pain. There are several which are capable of producing vasodilator effects.

Alcohol has been employed by Cook and Brown [164] in doses of 05. cc. per kilogram of body weight, by which it is possible to produce a high degree of vasodilatation which in controlled subjects approaches that obtained with fever and anesthesia. The duration is short and its effect on healing slight. The principal usefulness of this procedure is said to be in cases of arteriosclerosis with occlusion, when it is of great value in the relief of severe episodes of pain. Amputation can often be obviated or delayed, and the procedure is especially useful in those patients who present a poor surgical risk. It is more effective than morphine in the relief of pain while the patient is at rest. It may also at times reduce or eliminate the chill which follows the intravenous injection of foreign protein.

Theobromine or its compounds [165] administered in sufficiently large doses in some cases appears to be of value in producing more prolonged vasodilatation. Theophylline ethylene diamine has a similar effect. The principal value of these drugs is likewise seen in cases of arteriosclerosis obliterans in which vigorous measures are contraindicated. The drugs are not effective in all cases, but in a certain proportion they have been used successfully in the relief of symptoms, and with prolonged treatment less severe trophic lesions have healed. Intermittent claudication has been relieved in some cases, both of the arteriosclerosis and of the thrombo-angiitis obliterans variety.

Several recent reports have appeared on the use of papaverine in sudden arterial occlusion. If the experience of Denk [166] is confirmed by others, it is an important drug. Denk stated that the results of administration of papaverine equaled those following embolectomy, in pulmonary as well as in peripheral conditions. He has used it intravenously, repeated at short intervals (two to three hours) if necessary and continued at longer intervals for several days. If there is no relief of symptoms after the first or second injection none may be expected. In his experience, the drug was ineffective if used more than from two

164. Cook, E. N., and Brown, G. E.: The Vasodilating Effect of Ethyl Alcohol on the Peripheral Arteries, Proc. Staff Meet., Mayo Clin. **7**:449 (Aug. 3) 1932.

165. Scupham, G. W.: The Effect of Theobromine on Peripheral Vascular Diseases: Clinical Observation, Arch. Int. Med. **54**:685 (Nov.) 1934.

166. Denk, W.: Zur Behandlung der Arterien Embolie, München. med. Wchnschr. **81**:437 (March 23) 1934.

to four hours after the embolism occurred, and in advanced cases of arteriosclerosis the results were not as good as in cases in which there was relatively little degenerative disease.

Allen and McLean [167] report the use of papaverine in 1 case, in which "the return of circulation to the right leg as a result of treatment with papaverine was the most striking and dramatic" they had observed. They believe that the rapid improvement can be explained only by the relief of widespread arterial spasm initiated by sudden arterial occlusion. They state that its use is not contraindicated and in view of the prompt results obtained think it a valuable measure in addition to treatment by positive and negative pressure or embolectomy.

In addition to embolism de Takáts [104] has employed papaverine for the relief of vasospastic episodes of other types of obliterative disease.

Acetyl-beta-methylcholine has been found by Starr [168] to be a more effective drug than acetylcholine. It is a much more stable compound and produces more prolonged effects. It can be given, and is effective, both orally and subcutaneously. Its effects are similar to those following stimulation of the parasympathetic nerves, and it also causes peripheral vasodilatation. After subcutaneous injection it has a prompt and vigorous action. When administered orally its effects are milder. No serious toxic effects of the drug have been noted, and all effects can be immediately abolished by atropine.

Starr has found the drug effective in terminating paroxysmal tachycardia when given subcutaneously. The vascular spasm of Raynaud's disease was relieved or prevented by the action of the drug given by mouth when the spasm was excited by mild degrees of cold. It was ineffective when the exciting degree of cold was severe. It causes a rise in the cutaneous temperature of normal persons and in some persons with thrombo-angiitis obliterans, and gives some relief from pain in persons in the pregangrenous state of obstructive disease even though no evidence of vasodilatation is demonstrable. Page [169] states that the central mechanism plays an important part in the vasodilatator effect. He states that dilatation of the blood vessels of the hands and feet is so slight that it is disappointing from the point of view of therapy. The rise in temperature, he thinks, is inconsequential.

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167. Allen, E. V., and McLean, A. R.: The Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride: Report of a Case, Proc. Staff Meet., Mayo Clin. **10**:216 (April 3) 1935.

168. Starr, I., Jr.: Acetyl Beta Methyl Choline: III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease with a Discussion of Its Action in Other Conditions, Am. J. M. Sc. **186**:330 (Sept.) 1933.

169. Page, I. H.: Acetyl-Beta-Methylcholin (Mecholin): Observations Concerning Its Action on Blood Pressure, Skin Temperature and the Heart, as Exhibited by the Electrocardiogram of a Hypertensive Patient, Am. J. M. Sc. **189**: 55 (Jan.) 1935.

Goldsmith and Brown [170] are encouraged by indications of the usefulness of the drug as a vasodilatator, the safety in its use, the ease of administration and its prolonged effect.

Calcium has been suggested recently in the treatment of vasospastic disorders, particularly in those in which the Raynaud syndrome occurs, including scleroderma and some cases of thrombo-angiitis obliterans. Bernheim and London [171] comment on 4 mild atypical cases of the Raynaud syndrome in which improvement occurred with the patient on a program of high intake of calcium with a diet high in vitamins.

This idea has been carried on by Bernheim and Garlock.[129] They are of the opinion that calcium deficiency is an important factor in the etiology of angiospastic states. In mild cases of Raynaud's disease feeding the patient calcium improved the condition, and both in cases of Raynaud's disease and in cases of scleroderma parathyroidectomy with continued feeding of calcium postoperatively resulted in marked improvement.

Conwell [172] used parathyroid extract and calcium gluconate in 4 cases of thrombo-angiitis obliterans in which there was hypocalcemia. Marked improvement followed this procedure, even though other methods had not been successful.

Of the physical methods of treatment perhaps the most important advance has been the development of automatic apparatus by means of which prolonged treatment of obstructive vascular disease can be maintained by means of alternating positive and negative pressure applied to an extremity. This method, with some minor differences but much the same in principle, has been developed independently by Landis and Gibbon [173] and Reid and Hermann.[174] Since the original reports, several later ones have appeared from both sources.

The apparatus of Landis and Gibbon consists of an aluminum box into which the extremity is sealed by a rubber cuff. Alternating suc-

170. Goldsmith, Grace A.: The Vasodilating Effects of Acetyl β-Methylcholine, Proc. Staff Meet., Mayo Clin. **9**:337 (June 6) 1934.

171. Bernheim, Alice R., and London, Isabella M.: The Treatment of Spasmodic Vascular Disease of the Extremities of the Raynaud Type, Am. Heart J. **7**:588 (June) 1932.

172. Conwell, D. V.: The Treatment of Intermittent Claudication and Thrombo-Angiitis Obliterans with Parathyroid Extracts, J. Kansas M. Soc. **34**:457 (Dec.) 1933.

173. Landis, E. M., and Gibbon, J. H. Jr.: Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities, Proc. Soc. Exper. Biol. & Med. **30**:593, 1933; Effects of Alternate Suction and Pressure on Blood Flow to the Lower Extremities, J. Clin. Investigation **12**:9715, 1933.

174. Reid, M. R., and Hermann, L. G.: Treatment of Obliterative Vascular Diseases by Means of Intermittent Negative Pressure Environment, J. Med. **14**: 200, 1933. Hermann, L. G., and Reid, M. R.: Paevex (Passive Vascular Exercise) Treatment of Obliterative Arterial Diseases of the Extremities, ibid. **14**:524, 1933.

tion and pressure are applied by means of electrically driven pumps. The latest report of Landis and Hitzrot [175] indicates that with the technic employed by them rapid changes in pressure are accomplished for short periods. Suction at a negative pressure of 120 mm. of mercury is maintained for a period of twenty-five seconds followed by positive pressure of 80 mg. of mercury for a period of five seconds.

The Hermann and Reid [176] apparatus is likewise automatic. A glass boot is used for application about an extremity, so that it can be elevated or lowered. A rhythmic change in pressure can be applied from 80 mm. of mercury negative to 20 mm. of mercury positive at any selected rate of alternation. The changes in pressure occur more slowly than in the apparatus of Landis and Gibbon.

When treatment by this method is carried out frequently enough it causes the smaller arteries and arterioles to dilate and become sufficiently large to carry the collateral circulation about obliterated or badly diseased arteries.[176b] In all patients who received intensive treatment for two weeks or more, according to Hermann and Reid, there was a rise in cutaneous temperature when observed under controlled conditions. Much of the pain disappeared in more than 86 per cent of the cases, all of which were of the severe obstructive type. In a few only slight symptomatic relief was noted, and 1 patient stated that he was not relieved after three months of treatment.

The authors emphasize the point that treatment by passive vascular exercise [176b] should supplement the methods which experience has shown to be of value. This applies particularly to the prevention of infection and avoidance of the slightest injury.

Landis and Gibbon [178] have shown in normal subjects under carefully controlled conditions that the flow of blood as indicated by cutaneous temperature is greater in the limb exposed to variations of pressure and conclude that to obtain maximal effects on the flow of blood there should be relatively brief periods of suction, intermittent brief periods of pressure and diminished vasoconstrictor tone. The last is thought to be necessary in order to have the reservoir for the incoming blood as great as possible. This these workers accomplish by enclosing one arm in an electric heating pad kept warm enough to produce slight general sweating.[178]

175. Landis E. M., and Hitzrot, L. H.: The Clinical Value of Alternate Suction and Pressure in the Treatment of Advanced Peripheral Vascular Disease, Am. J. M. Sc. **189**:305 (March) 1935.

176. (*a*) Reid, M. R., and Hermann, L. G.: Conservative Treatment of the Arteriosclerotic Peripheral Vascular Disease, Ann. Surg. **100**:750 (Oct.) 1934. (*b*) Hermann, L. G., and Reid, M. R.: Passive Vascular Exercises: Treatment of Peripheral Obliterative Arterial Diseases by Rhythmic Alternation of Environmental Pressure, Arch. Surg. **29**:697 (Nov.) 1934.

Even in cases of peripheral vascular disease which has advanced to the place where there is no increase in circulation with the abolition of vasoconstrictor tone, Landis [177] has found it possible to increase the blood flow by this method. Cyanosis and pain while the patient is at rest are diminished at least temporarily, and in some cases indolent superficial ulcers have healed. In a more recent publication Landis and Hitzrot [175] report on the results in 29 cases. In most of these cases the patients had been treated previously by the usual methods without success. After treatment by suction and pressure, the authors were able to record the results in 20 patients as good. They regard this as significant. The findings in this group confirm those previously reported. Pain of ischemia while the patient was at rest was usually relieved during the course of treatment and gradually became less severe in the intervals between. Lasting relief was not observed in the presence of deeply extending gangrene, large sloughs or osteomyelitis. Ulcers began to heal soon after the institution of treatment. Intermittent claudication was benefited.

Landis and Hitzrot state that this form of therapy must be applied with caution, and they advise small changes in pressure at first. The presence of acute infection or abscesses is an absolute contraindication. If carefully used the method is of distinct value and is of service by increasing the flow of blood temporarily during episodes of pain or ulceration so that time is gained for the development of collateral circulation.

Shipley and Yeager [178] obtained good results. They extended the treatment to include gangrene caused by frost-bite, arthritis, ununited fractures and other conditions.

De Takáts [179] used the method of Hermann and Reid. He agrees that a temporary increase in blood flow can be obtained in the presence of organic obstruction even in the case of a peripheral vascular bed which can hardly dilate. Improvement is obtainable in patients for whom no other therapy than amputation is helpful. He has given as his impression that the cases in which response is best are those in which there is involvement of the smaller vessels, in contrast to the experience of Hermann and Reid.[176a] Although de Takáts' experience was not satisfactory with the group of cases of sudden organic occlusion, he is of the opinion that if used early this form of treatment may tide over periods of

177. Landis, E. M.: Observations on the Diagnosis and Treatment of Peripheral Vascular Disease, Ann. Int. Med. **8**:282 (Sept.) 1934.

178. Shipley, A. M., and Yeager, G. H.: Passive Vascular Exercise in the Treatment of Peripheral Circulatory Disease, Surg., Gynec. & Obst. **59**:480 (Sept.) 1934.

179. de Takáts, Géza: Obliterative Vascular Disease, J. A. M. A. **103**:1920 (Dec. 22) 1934.

crisis with a minimal loss of tissue. The effect is essentially that of release of spasm in the collateral circulation. He warns against the use of this method in case of infections and particularly in cases of venous thrombosis, as well as in those of the infectious type of diabetic gangrene. Especially in acute cases of venous thrombosis in which temporary arterial spasm sometimes occurs is this type of treatment to be avoided.

SURGICAL TREATMENT: A CRITICAL REVIEW

By Dr. de Takáts

An increasingly conservative attitude in the surgical treatment of peripheral vascular disease is unmistakable. This is due, first, to an earlier recognition of disorders of the peripheral circulation. Only in the last few years have patients been seen and treated before they arrived at the terminal stage of gangrene. Second, a more thorough understanding of the conditions which cause impaired circulation lead to the adoption of surgical procedures which are intended to improve or correct the perverted function of the blood vessels. Third, with a better insight into nature's methods of compensating for impairment of circulation, the surgeon may attempt to fit his procedure to the natural methods of repair instead of interfering with them.

The considerable amount of work which has accumulated in the last few years may be grouped under three headings, namely: (1) surgical efforts to improve impaired circulation, (2) surgical efforts to alleviate pain in cases of peripheral vascular disease and (3) surgical methods of removing nonviable parts at the optimal time and at the optimal level.

SURGICAL ATTEMPTS TO IMPROVE PERIPHERAL CIRCULATION

Ligation of a Vein.—The origin and development of the therapeutic procedure of occluding the concomitant vein of an obstructed artery dates from experiences gathered in the World War.[180] Experimentally, Brooks and his associates[181] have demonstrated in repeated series of observations that the simultaneous ligation of the vein protects from gangrene an extremity the main artery of which has been tied. Previous

180. Sehrt, E.: Ueber die künstliche Blutleere von Gliedmassen der unterer Körperhälfte sowie über die Ursache der Gangrän des Gliedes nach Unterbindung der Arterie allein, Med. Klin. **12**:1338, 1916. Makins, G.: Hunterian Oration, 1917, Lancet **1**:249, 1917. Propping, K.: Ueber die Ursachen der Gangrän nach Unterbindung grosser Arterien, München. med. Wchnschr. **65**:388, 1918.

181. Brooks, B.; Johnson, G. S., and Kerthey, J. A., Jr.: Simultaneous Vein Ligation: Experimental Study of Effect of Ligation of Concomitant Vein on Incidence of Gangrene Following Arterial Obstruction, Surg., Gynec. & Obst. **59**:496, 1934.

to the emphasis given to this procedure by Makins of the allied armies and Propping of the German army, a number of individual reports of ligation of both an artery and the corresponding vein were made, but this procedure was carried out of necessity and with considerable trepidation as to the increased incidence of gangrene.

There is considerable disagreement both in the experimental and in the clinical studies as to the mechanism and value of the procedure. The following changes have been reported to take place after ligation of the vein when the artery was simultaneously occluded: increased systolic blood pressure,[182] increased venous pressure,[182] diminished volume flow of blood,[182a] increased surface and deep temperature,[183] increased collateral circulatory bed [184] and diminished incidence of gangrene.[185] Clinically, Oppel, Lilienthal, Willy Meyer, Ginsberg, Morton and Pearse, Brooks and Johnson and Van Gorder and Silbert report favorably on the use of this procedure for relief of chronic arterial obstructions in such diseases as arteriosclerosis and thrombo-angiitis obliterans. Silbert [186] reports 16 cases, evaluates the results carefully and says that in 9 cases a definite benefit has been obtained. He defers a final conclusion until greater experience has been obtained. On the other hand, the experiments of Theis [187] and Mulvihill, Harvey and Doroszka [188] and the clinical observation of McNealy [189] do not indicate any beneficial effects from simultaneous ligation of a vein. A critical review of the literature was published in 1931 by Mulvihill, Harvey and Doroszka,[188] who concluded that the literature on experimental ligation did not furnish any definitely proved, sound physiologic basis for this procedure and that the ligation of an artery in the lower extremity of man is not followed

182. (*a*) Brooks, B., and Martin, K. A.: Simultaneous Ligation of Vein and Artery: An Experimental Study, J. A. M. A. **80**:1678 (June 9) 1923. (*b*) Holman, E., and Edwards, M. E.: A New Principle in the Surgery of the Large Arteries, ibid. **88**:909 (March 19) 1927.

183. Morton, J. J., and Pearse, H. E.: Temperature Effect of Popliteal Vein Ligation in Thrombo-Angiitis Obliterans and Arteriosclerosis, Ann. Surg. **88**:233, 1928.

184. Pearse, H. E.: A New Explanation of the Improved Results Following Ligation of Both Artery and Vein, Ann. Surg. **81**:850, 1925.

185. Brooks, Johnson and Kerthey.[181] Holman and Edwards.[182b]

186. Silbert, S.: The Value of Femoral Vein Ligation in Chronic Arterial Obstruction, in Contributions to the Medical Sciences in Honor of Dr. Emanual Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 1079.

187. Theis, F. V.: Ligation of Artery and Concomitant Vein in Operations on the Large Blood Vessels, Arch. Surg. **17**:244 (Aug.) 1928.

188. Mulvihill, D. A.; Harvey, S. C., and Doroszka, V.: Simultaneous Ligation of Vein in Ligation of Large Arteries, Am. J. Surg. **13**:431, 1931.

189. McNealy, R. W.: The Place of Elective Vein Ligation, Surg., Gynec. & Obst. **40**:45, 1925.

by a very high incidence of gangrene; in fact, it nearly approaches the 6.6 per cent given by Halsted [190] as the incidence of gangrene in cases in which ligation of the common iliac artery was carried out.

The confusion and conflicts of opinion arise chiefly from the fact that different types of patients were subjected to ligation of the vein. In cases of arteriovenous aneurysm the ligation of both the artery and the vein, preferably proximally and distally, is a well established procedure.[191] In acute cases of vascular occlusion resulting from a traumatic injury of the artery it is worth while considering that the temporary increase in venous pressure following ligation of the vein may be of aid in the critical period of developing collateral circulation. It may also release, at least in part, the spasm of the collateral vessel occurring in cases of acute vascular occlusion. In cases of chronic vascular occlusion, however, the possible benefits derived from this procedure are questionable. In addition, there is a possibility of a descending thrombosis reaching as far as the small veins, which certainly does not favor collateral circulation and which may even predispose to moist gangrene.

Generally speaking, ligation of a vein has not been of definite demonstrable benefit in cases of chronic vascular disease. Its main indication lies in the surgical procedures for aneurysms.

Periarterial Sympathectomy.—The stripping of the adventitia of the main nutrient artery of a part was chiefly popularized by Leriche.[192] His initial publication stimulated a vast amount of work in continental Europe, and with undue enthusiasm a wide variety of clinical conditions have been included among the indications. According to reports by his school and a group of German investigators,[193] this operation has been successful in cases of causalgia, Raynaud's disease, trophic and traumatic ulcer, various kinds of cutaneous edema and cutaneous diseases, arthritis and delayed healing of bone. Later, a certain skepticism in regard to the permanent benefits became evident. Among others, Bernheim [194] reported on 30 cases of periarterial sympathectomy for circulatory disturbances of the extremities. In 11 the operation was regarded as a success and in 17 as a failure.

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190. Halsted, W. S.: The Effect of Ligation of the Common Iliac Artery on the Circulation and Function of the Lower Extremity, Bull. Johns Hopkins Hosp. **22**:191, 1912.

191. Footnotes 180 and 189.

192. Leriche, R., and Heitz, J.: Des effets physiologiques de la sympathectomie périphérique, Compt. rend. Soc. de biol. **80**:66, 1917.

193. Brüning, F., and Forster, E.: Periarterielle Sympathektomie, Zentralbl. f. Chir. **49**:913, 1922.

194. Bernheim, B. M.: Periarterial Sympathectomy in Circulatory Disorders of the Extremities, Surg., Gynec. & Obst. **50**:456, 1930.

Reports of similar and contradictory character could be multiplied almost indefinitely. More recently, a small group of investigators[195] have brought forth both experimental and clinical evidence that this operation increases vascularity and accelerates the formation of callus and bony union. Colp, Kasabach and Mage believe that a further trial of the operation is justifiable in cases of recent fracture in those regions in which delay in union is characteristic and in those cases of fracture in which union appears to be delayed. Fontaine and Herrmann describe a disease entity which is characterized by the loss of motor function, characteristic patchy and later diffuse osteoporosis and a coexistence of vasomotor disturbances and great pain. It is not easy to differentiate these cases from those of Sudeck's reflex atrophy or from those of causalgia. In most cases, at least in the early stage, there are hyperemia and increased oscillations. Fontaine and Herrmann advise periarterial sympathectomy if the disease is limited to the distal parts of the extremity but cervical and lumbar ramisection for the extensive forms of the disease.

In spite of these favorable reports, most writers agree that hyperemia produced by periarterial sympathectomy is evanescent and that whatever effect can be obtained, such as more rapid formation of callus, healing of ulcers and taking of skin grafts, must be accomplished within from two to three weeks. It is difficult to see, in the light of careful anatomic studies,[196] how stripping of a short segment of an artery can effect the innervation of the arterial tree, as fibers of both sympathetic and spinal origin join the peripheral arteries in segments from branches of the peripheral nerves. Numerous attempts have been made to explain the results obtained by this operation. Leriche and Robeneau[197] suggest that the vasomotor effects of a single unilateral operation extend to all four extremities and that vasomotor reflexes are initiated from the denuded artery and are afferent. The subsidence of pain has also been explained by various ingenious theories.[4] Epicritically one may say that neither theoretical considerations nor uncontrovertible clinical evidence supports the lasting value of periarterial sympathectomy. The only exception to this may be the occasional case in which a fibrosed artery or vein maintains reflectoric vasomotor phenomena. The strip-

195. Colp, R.; Kasabach, H., and Mage, S.: Periarterial Sympathectomy in Fractures: An Experimental Study, Arch. Surg. **27**:658 (Oct.) 1933. Fontaine, R., and Herrmann, L. G.: Post-Traumatic Painful Osteoporosis, Ann. Surg. **97**:26, 1933.

196. Kramer, J. G., and Todd, T. W.: The Distribution of Nerves to the Arteries of the Arm, Anat. Rec. **8**:243, 1914. Potts, L. W.: The Distribution of Nerves to the Arteries of the Leg, Anat. Anz. **47**:138, 1915.

197. Leriche, R., and Robeneau, F.: Indications et résultats de la sympathectomie périartérielle dans la chirurgie des membres, Paris chir. **19**:191, 1927.

ping of such an obliterated vessel does release spasm of the vessel.[198] This question will be discussed further under the section and resection of obliterated vascular segments.

Leriche and his associates [199] review their results with various types of sympathectomy for chronic ulcers of the leg. It is apparent that their original claims have not been substantiated. Fair results have been obtained in cases of posttraumatic ulceration, excellent results in cases of varicose ulceration and poor results in cases of postphlebitic ulceration. The sympathectomies were combined with skin grafting. In the phlebitic group two fatal cases of embolism occurred.

Arterial Ligation.—Lewis and Reichert [200] propose ligation of the femoral artery just distal to the origin of the deep femoral artery in patients with Buerger's disease, with the idea of stimulating collateral circulation and speeding it up to keep ahead of the impending gangrene. They report 1 case. In a later article [201] 7 cases are reported. In 4 cases there was distinct improvement; in 2 cases in which gangrene was present at the time of the operation, amputation became necessary, and in 1 case hemiplegia and death followed the operation.

Lewis explained the relief from pain as a result of putting the inflamed artery at rest and partly as a result of increasing the collateral circulation. That a diminution of the intravascular tension relieves vascular pain is often experienced after ligation of the saphenous artery above a painful area of phlebitis. But the fact remains that the blood flow is actually cut down by ligation of the femoral artery and that the procedure, especially in cases of thrombo-angiitis obliterans, may lead to a sudden massive thrombosis distal to the ligature. That a certain transitory effect on the periarterial sympathetic system is operating in all arterial ligations was the early observation of Jaboulay.[202]

Arterial Excision (Arteriectomy).—In 1915 Leriche resected an obliterated arterial trunk in a patient suffering from causalgia. The pain disappeared, and no relapse had occurred for seventeen months. Since this time, a number of communications have appeared from Leriche and his pupils. These are summarized with their present indications, experi-

198. Leriche, R., and Fontaine, R.: Experimental Researches on Vasomotricity, Am. J. Surg. **85**:641, 1927.

199. Leriche, R.; Fontaine, R., and Maitre, R.: Résultats éloignés du traitements des ulcéres jambes par les opérations sympathiques combinées aux greffes cutanées d'après 52 observations, J. de chir. **45**:689, 1935.

200. Lewis, D., and Reichert, F. L.: Collateral Circulation in Thrombo-Angiitis Obliterans: An Indication for Ligation of the Femoral Artery Just Distal to Profunda, J. A. M. A. **87**:302 (July 31) 1926.

201. Lewis, D.: Spontaneous Gangrene of the Extremities, Arch. Surg. **15**: 613 (Oct.) 1927.

202. Jaboulay, cited by Kuntz, A.: The Autonomic Nervous System, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 539.

mental and clinical results, in a recent monograph.[203] Experimentally, resection of the femoral or external iliac artery produced a smaller drop in the temperature of the dog's limb than if the same vessel had simply been ligated. When the common iliac artery was tied moist gangrene occurred in a large percentage of cases and occasionally death, whereas resection of the same artery resulted in dry gangrene of some digits that readily healed after self-amputation.

Leriche states that the type of arteritis which follows trauma, local compression, freezing and localized emboli is suitable for arteriectomy. This interrupts the reflectoric vasoconstriction which originates in the periarteritic fibrosis and which is responsible for the cyanosis, sensitivity to cold and trophic changes. The diagnosis of such localized inflammation of a single artery was made by arteriographic examination.

It is obvious that such an operation is not indicated in the majority of cases of peripheral vascular disease. However, on the basis of experimental evidence it must be admitted that in the occasional case of accurately localized thrombosis the excision of such an irritating focus may relieve vasomotor phenomena. Because of this reflex, vasoconstriction can be effectively interrupted by sympathetic ganglionectomy, and the scope of this method is further restricted.

Sympathetic Ramisection.—In 1924 practically simultaneously this operation was proposed in three different countries. In Germany von Gaza described it for "neuropathic abdominal dysfunctions." In Australia Royle advocated it for spastic paraplegia, whereas in France Leriche wished to modify painful vasomotor and trophic phenomena. Theoretically this operation would be the optimal one to deprive an extremity of its vasomotor innervation, because it interrupts the gray rami connecting the ganglionated trunk with the peripheral nerves and leaves the ganglions with their visceral innervation intact. It has gradually become clear, however, that (1) the operation can practically never be complete, as gray and white rami are not easy to distinguish and there are innumerable anatomic variations and a large number of the gray rami supplying the leg arise from the sacral ganglions in the pelvis so that complete ramisection is impossible; (2) the postganglionic fibers which are cut by such an operation readily regenerate, and (3) the much feared removal of the sympathetic ganglions and intervening trunk does not produce lasting or significant changes in the normal viscera deprived of their sympathetic nerve supply. On the contrary, when evidence of sympathetic overbalance is demonstrable the condition is benefited by ganglionectomy.

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203. Leriche, R., and Stricker, P.: L'artériectomie dans les artérites oblitérantes: Etude expérimentale et thérapeutique, Paris, Masson & Cie, 1933.

For these reasons ramisection is thought to be improved by the addition of section of the sympathetic trunk, thus interrupting the preganglionic outflow from the cord.[204] Although this operation gives better results than ramisectomy alone, it is justly criticized on two grounds:[205] First, the trunk, if merely cut across, is capable of regeneration, and the effects may be temporary, and, second, it has been shown ever since the time of Claude Bernard that peripheral vasodilatation is maximal only if the cells of the postganglionic fibers are removed.

The only satisfactory method, therefore, of removing the sympathetic supply to a limb is by ganglionectomy. As previously stated, the loss of visceral branches seems to have no ill effect on the patient. However, Danielopolu and his co-workers[206] maintain that the removal of the stellate ganglion modifies the chromotropic and inotropic properties of the myocardium. Clinically, in many hundreds of cases in which bilateral cervicodorsal sympathectomy has been carried out, ill effects have not been observed.

Sympathetic Ganglionectomy.—This operation has gradually developed from an increasing conviction that lesser procedures, such as periarterial sympathectomy or ramisection, do not result in complete or lasting sympathetic denervation. Diez,[207] Adson and Brown,[208] Flothow and Swift,[209] Stammers[210] and Telford and Stopford[211] have observed large series. With increasing experience in sympathectomy, Diez in Buenos Aires and Adson of the Mayo Clinic postulate the treatment

204. Royle, N. D.: Sympathetic Trunk Section: A New Operation for Raynaud's Disease and Spastic Paralysis of the Upper Limb, M. J. Australia **2**:436, 1928.

205. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, Baltimore, William Wood & Company, 1934, p. 64.

206. Danielopolu, D.; Marcou, I., and Proca, G. G.: Sur la physiologie du ganglion étoilé: modifications des propriétés fondamentales du myocarde provoquées par l'extirpation unilatérale ou bilatérale du premiere ganglion thoracique chez le chien, le coeur étant normal ou expérimentalment altéré, Arch. de mal. du coeur **22**:769, 1929.

207. Diez, J.: La tromboangeitis obliterante, Buenos Aires, El Ateneo, 1934.

208. Adson, A., and Brown, G. E.: The Treatment of Raynaud's Disease of the Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, Surg., Gynec. & Obst. **48**:577, 1929. Brown, G. E. Thrombo-Angiitis Obliterans: Buerger's Disease, ibid. **58**:297, 1934.

209. Flothow, P. G., and Swift, G. W.: Surgery of the Sympathetic Nervous System: Review of 100 Sympathetic Ganglionectomies, Am. J. Surg. **21**:345, 1933.

210. Stammers, F. A. R.: Some Experiences with Sympathetic Ganglionectomy, Brit. J. Surg. **20**:67, 1932.

211. Telford, E. D., and Stopford, J. S. B.: Remarks on the Results of Lumbar Sympathectomy in Thrombo-Angiitis Obliterans, Brit. M. J. **1**:173, 1933.

of peripheral vascular disease by sympathetic denervation which is as complete as possible. For the sympathetic denervation of the upper extremity, as Kuntz [212] points out, it is necessary to cut the dorsal sympathetic trunk below the second dorsal ganglion because of a frequently communicating branch from the second ganglion to the first thoracic nerve. On the basis of these observations Adson evolved his technic of cervicodorsal sympathectomy from a posterior approach.[213] It also became evident from observations of Diez and those on my unreported cases that removal of the inferior cervical ganglion without the intermediate ganglion may lead to incomplete denervation or to Horner's syndrome, indicating that connections are possible between the cord and the intermediate ganglion. The anterior approach of Gask,[214] which permits exposure and removal of the intermediate and stellate ganglions with a section of the thoracic chain below the second ganglion, seems anatomically less injurious. Other technical modifications by Flothow and Swift,[209] Leriche and Fontaine [215] and White, Smithwick, Allen and Mixter [216] illustrate that the surgical approach for cervicothoracic sympathectomy is still in the process of development, with an unmistakable effort at complete denervation. So far, Gask's method seems the most satisfactory.

For sympathetic denervation of the lower extremities the removal of the second, third and fourth lumbar ganglions is postulated through the anterior, transperitoneal,[217] anterolateral [218] and original posterior retroperitoneal approach.[219] For bilateral sympathectomy the transperitoneal

212. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, Arch. Surg. **15**: 871 (Nov.) 1927.

213. Adson, A. W.: (*a*) Cervicothoracic Ganglionectomy, Trunk Resection and Ramisection by the Posterior Intrathoracic Approach, Am. J. Surg. **11**:227, 1931; (*b*) Changes in Technique of Cervicothoracic Ganglionectomy and Trunk Resection, ibid. **23**:287, 1934.

214. Gask, G. E.: The Surgery of the Sympathetic Nervous System, Brit. J. Surg. **21**:113, 1933.

215. Leriche, R., and Fontaine, R.: Technique de l'ablation du ganglion etoilé, J. de chir. **41**:353, 1933.

216. White, J. C.; Smithwick, R. H.; Allen, A. W., and Mixter, W. J.: A New Muscle-Splitting Incision for Resection of the Upper Thoracic Sympathetic Ganglia, Surg., Gynec. & Obst. **56**:651, 1933.

217. Adson, A. W., and Brown, G. E.: Treatment of Raynaud's Disease by Lumbar Ramisection and Ganglionectomy and Perivascular Sympathetic Neurectomy of the Common Iliacs, J. A. M. A. **84**:1908 (June 20) 1925.

218. (*a*) Rieder, W.: Resection der die unteren Extremitäten versorgenden Rami communicantes, Chirurg **5**:100, 1933. (*b*) Livingston, W. K.: The Clinical Aspects of Visceral Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1935. Flothow and Swift.[209]

219. Royle, N. D.: The Treatment of Spastic Paralysis by Sympathetic Ramisection: Experimental Basis and Clinical Results, Surg., Gynec. & Obst. **39**:701, 1924.

approach is most logical. In unilateral sympathectomy an anterolateral approach with the area under local anesthesia [207] seems the safest and the one that allows exposure of the chain from the renal to the external iliac artery.

The results to be expected from sympathetic ganglionectomy in peripheral vascular disease may be gaged before the operation by the use of various tests for organic or spastic vascular occlusion. Whatever test is used, it only measures the reserve capacity of the peripheral vascular bed following immediate inhibition of the vasoconstrictor nerves. These tests do not indicate the end-results, as they do not allow time for the degeneration of postganglionic fibers or for the restoration of an intrinsic tonus of the wall of the vessel.

The physiologic effects of complete sympathetic denervation have been described as follows: There is an absence of sweating in the denervated area, which can be tested by Minor's method with starch and iodine [220] or more conveniently by the use of cobaltous chloride.[221] For more exact determinations the measurement of resistance of the skin can be employed.[222] As the nerve fibers which control sweating and vasomotor impulses run a parallel course these tests for sweating constitute a simple clinical estimation of the completeness of sympathectomy.

The vasomotor phenomena following sympathectomy in extremities with normal blood vessels run a biphasic course. An immediate reaction, which lasts from three to twenty-one days, consists of flushing of the skin and increased pulsations,[205] increased oscillometric curves,[207] increased plethysmographic curves of the digits,[15] distention and pulsation of an enlarged capillary bed,[223] increased elimination of heat and a rise in surface temperature.[224] In a second stage, which usually begins in the second or third week, the skin becomes pale, the visible capillaries are contracted but show a rapid flow and the plethysmographic tracings of the digits show a return to the preoperative rate of pulsation. The vessels regain their tonus, a fact first demonstrated in 1874.[225]

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220. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, Deutsche Ztschr. f. Nervenh. **101**:302, 1928.

221. Roth, Grace M.: A Clinical Test for Sweating, Proc. Staff Meet., Mayo Clin. **10**:383, 1935.

222. Soloman, A. P., and Fentress, T. L.: Galvanic Skin Reflex and Blood Pressure Reactions in Psychoneuroses, J. Nerv. & Ment. Dis. **80**:163, 1934.

223. Brown, G. E.: Observations on the Surface Capillaries in Men Following Cervicothoracic Sympathetic Ganglionectomy, J. Clin. Investigation **9**:115, 1930.

224. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, Arch. Neurol. & Psychiat. **22**:322 (Aug.) 1929.

225. Goltz, F., and Freusberg, F.: Arch. f. exper. Path. & Pharmacol. **9**:174, 1874.

When preganglionic fibers have been sectioned, degeneration of the postganglionic fibers does not take place, and the erector pilae muscles of the hair follicles can be made to contract and produce goose-flesh on direct stimulation with a faradic current,[226] which, however, is not possible when postganglionic section has been performed. Thus, after cervicothoracic sympathectomy, direct pilomotor response cannot be elicited on the arm but is present on the face, because the postganglionic fibers arising in the intact superior cervical ganglion remain intact.

Another way to differentiate between preganglionic and postganglionic section is by the test for sensitivity to epinephrine, first demonstrated on the iris by Meltzer and Auer,[227] but recently emphasized and elaborated in the case of peripheral vessels by James White and his co-workers.[17] They have shown that an intravenous injection of 1 part of epinephrine in 250,000 parts of physiologic solution of sodium chloride injected at a rate of from 40 to 60 drops a minute will cause striking vasoconstriction in the extremities, with complete postganglionic denervation, but not when the operation is incomplete or if the section is preganglionic.

Clearcut evidence of increased blood flow in the sympathectomized extremity, which seems to persist indefinitely, has been furnished by Herrick, Essex and Baldes,[228] who measured the minute volume in the femoral artery of the dog with Rein's *Thermostromuhr* and found it to be about twice as great in the sympathectomized extremity as in the control extremity. In addition, Gaskell,[229] Hinsey [230] and Theis [231] have brought forward indirect experimental evidence of persistently increased blood flow after a sympathectomy. Measurements of blood flow with the modification of the method of Hewlett and Van Zwaluwenburg have been made in a number of cases on the sympathectomized extremity by Diez.[207] His measurements on man are the most clearcut evidence for permanently increased blood flow in the sympathectomized limb.

Results of sympathetic ganglionectomy for various vasomotor disturbances are gradually accumulating. There is agreement in the litera-

226. Lewis, T., and Marvin, H. M.: Observations upon a Pilomotor Reaction in Response to Faradism, J. Physiol. **64**:87, 1927.

227. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil-Dilation Caused by Adrenalin, Am. J. Physiol. **11**:28, 1904.

228. Herrick, J. F.; Essex, H. E., and Baldes, E. J.: The Effect of Lumbar Sympathectomy on the Flow of Blood in the Femoral Artery of the Dog, Am. J. Physiol. **101**:213, 1932.

229. Gaskell, W. H.: The Involuntary Nervous System, New York, Longmans, Green & Co., 1916.

230. Hinsey, J. L.: Observations on Skin Temperatures in Hind Limbs Deprived of Their Sensory and Sympathetic Nerve Supply, Am. J. Physiol. **109**:53, 1934.

231. Theis, F. V.: The Effect of Sympathetic Neurectomy on the Collateral Arterial Circulation of the Extremities, Surg., Gynec. & Obst. **57**:737, 1933.

ture that (1) sympathectomies on the lower extremities are generally more successful than those on the upper extremities;[232] (2) that the early stage of Raynaud's disease, in which secondary obliteration of the digital or even larger vessels has not yet taken place,[233] is the favorable stage for surgical intervention, and (3) that recurrences do occur, chiefly on the upper extremities, when evidence of organic involvement is available.

The causes of failure of sympathectomy in cases of Raynaud's disease have been carefully analyzed by James White in his recent monograph.[234] Failure may be due to (1) incomplete denervation, which is more apt to occur in operations on the upper extremities, (2) a late stage in the course of the disease, in which obliterative arterial changes are present, and (3) sensitization of the completely denervated limb to epinephrine when postganglionic degeneration of the sympathetic fibers has taken place. Better results on the lower extremity are explained by the fact that after complete cervicothoracic ganglionectomy all postganglionic vasoconstrictor neurons degenerate and render the digital vessels highly sensitive, whereas, following the resection of the second, third and fourth lumbar ganglions, only the last neurons to the femoral and obturator nerves degenerate, while the postganglionic neurons to the sciatic nerve, which originate in ganglion cells of the fourth lumbar to the third sacral ganglion, are unaffected, and here a preganglionic section has taken place.

From these considerations one might draw the inference that preganglionic section would be desirable for the upper extremity, but in order for this to be complete it would necessitate section of the anterior roots of the four upper dorsal segments.

Contrary to this opinion, Livingston tries to accomplish complete postganglionic section and degeneration. He suggests that an important cell station for the upper extremity may be found at the third thoracic ganglion, and removal of this structure would produce the most complete vasodilatation of the upper extremity. This operation clearly resembles then Royle's section of the trunk, which often leaves preganglionic fibers from cord to stellate or from cord to intermediate ganglion unsectioned.

At present, available evidence both from the anatomic and from the physiologic standpoint tends to show that the removal of the intermediate, inferior cervical and first and second thoracic ganglions gives

232. Telford, E. D.: Sympathectomy: A Review of 100 Operations, Lancet **1**:444, 1934. Adson.[213] Gask.[214] Livingston.[218b]

233. Leriche, R., and Fontaine, R.: Sur le nature de la maladie de Raynaud, Presse méd. **40**:1921, 1932. Spurling, Jelsma and Rogers.[131]

234. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935.

the most complete denervation for the upper extremities, and the excision of the second, third and fourth lumbar ganglions with the intervening trunk, the best denervation for the lower extremity. It is true that Oughterson, Harvey and Richter [235] have shown that following a typical lumbar sympathectomy vasodilatation is not complete unless the sacral ganglions are blocked. Nevertheless, for practical purposes the excision of the sacral sympathetic chain is unnecessary.

With spasms of the secondary vessel of central or reflectoric origin, such as those which occur in cases of anterior poliomyelitis,[236] of traumatic injuries to the spinal cord[234] and of lesions of the pyramidal tract without muscular atrophy,[234] the circulatory improvement is striking and permanent, although muscle spasticity is unrelieved. In experimental animals, when gangrene is threatened following arterial ligature or sudden thrombosis, inhibition of collateral spasm has saved the limb.[237] In patients, however, the block of the prevertebral chain with procaine hydrochloride, to be discussed later, is simpler and is equally effective in its temporary effects.

Most controversy centers about the treatment of thrombo-angiitis obliterans by sympathetic ganglionectomy. Diez [207] reports the cases of 150 patients and Adson the cases of over 100 patients with Buerger's disease on whom sympathectomy has been performed. In the former group there were 7 deaths: 2 of thrombosis of the abdominal aorta, 1 of a pulmonary abscess, 3 of bronchopneumonia and 1 of paralytic ileus. Diez attributes these to the use of general or spinal anesthesia and reports no deaths in the last series of 21 cases in which lumbar sympathectomy was carried out with the area under local anesthesia. In Adson's 6 fatal cases cardiovascular complications were prevalent. As to results, Diez reports recurrence or failure in 12 per cent of his total series, which dropped to 5 per cent in the last group of patients. Adson's results have been analyzed by Brown.[213b] They are less favorable than those of Diez and also of those of Silbert,[24] who reports the largest percentage of cures obtained by his conservative treatment.

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235. Oughterson, A. W.; Harvey, S. C., and Richter, H. G.: Observations on the Sympathetic Pathways, Ann. Surg. **96**:744, 1932.

236. Telford, E. D., and Stopford, J. S. B.: Some Experiences with Sympathectomy in Anterior Poliomyelitis, Brit. M. J. **2**:770, 1933.

237. Stricker, P., and Orban, F.: Recherches expérimentales sur la thrombose artérielle les artérites, la gangrène et sur le valeur comparée des ligatures artérielles et des artériectomies, J. de chir. **36**:697, 1930. Reickert, F. L.: Thermal Changes in Denervated and Sympathectomized Limbs With and Without Arterial Ligation, Proc. Soc. Exper. Biol. & Med. **29**:473, 1932. Oughterson, Harvey and Richter.[235] Theis.[231]

The attitude of Allen,[238] Livingston,[218b] and Gask and Ross [205] has been more conservative. The difficulty of treating patients with Buerger's disease by sympathectomy is due not only to the fact that in the late stages very little spasm is evident and a diffuse arteriolar involvement is exhibited, but to the facts that the disease in the extremities is not arrested by sympathectomy and acute thrombotic occlusion with subsequent gangrene may occur in a previously sympathectomized lower extremity. While the absence of reflex vasoconstriction in the suddenly occluded limb is of definite benefit, the reserve capacity of the collateral bed is so small that the inhibition of the collateral spasm cannot make much difference. Finally, as some of these patients show vascular involvement in the viscera, heart, brain and spinal cord, the operation cannot be expected to effect a cure.

So long as relief from pain in the extremities, excluding amputation, can be obtained by other measures, such as will be discussed later, sympathectomy in patients with Buerger's disease is best limited to the upper extremities, when digital gangrene and intractable pain are present. Here peripheral injections of alcohol are not feasible, and the available collateral bed is so extensive that a certain stabilizing effect on the disease may be observed. The operation may offer quick demarcation of the parts, rapid healing and, often, relief from pain. The disease itself must be treated as a general systemic disturbance.

In ultimate analysis the results from sympathectomy in cases of Buerger's disease are not striking, and the mortality rate, which is negligible if the operation is performed for other conditions, is approximately 6 per cent. That sometimes striking results are obtained in chronic cases of endarteritis obliterans in the healed stage should be emphasized. In such cases spasm of the vessels is maintained from the plexuses of the periarterial nerves. Hence, the importance of distinguishing this type of vascular obliteration from that of Buerger's disease.[104]

Embolectomy.—When the diagnosis of arterial thrombosis can be reasonably excluded and when the patient has been observed from six to ten hours after the sudden occlusion, embolectomy in a peripheral artery is justly considered. Pearse [101] has given a complete review and analysis of the location of emboli and their incidence in 272 cases reported in the literature. The axillary and brachial arteries in the upper extremity, the aorta and the common iliac, femoral and popliteal arteries of the lower extremity are the most common sites of embolism. The prognosis depends on the cardiovascular status of the patient, on

238. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thrombo-Angiitis Obliterans by Desensitization of Peripheral Sensory Nerves, Ann. Surg. **96**:867, 1932.

the extent of the collateral circulation at the obstructed level, on the early diagnosis and on operation during the early stage. Only a few hours are required before secondary arterial thrombi may occlude the peripheral branches of the artery. Also, the wall of the vessel reacts to emboli, so that a secondary thrombus may occur at the site of the removed embolus. Nevertheless, the collective review of the results of Pearse embolectomies performed within the first ten hours shows that the operation was successful on the upper extremities in 47 per cent of the cases, on the lower extremities in 40 per cent and in the pelvis in 31 per cent. Over half the patients subjected to embolectomy died within a month of the operation. This mortality was due either to the primary systemic disease, which was responsible for the embolism, or to emboli which later appeared in vital structures.

Two significant conservative measures, treatment by alternating negative pressure [239] and the intravenous injections of papaverine,[166] or the two methods combined, are worthy of trial before embolectomy is decided on.

Adrenalectomy and Adrenal Denervation.—In their report at the forty-third session of the French surgical congress Leibovici and Stricker [240] conclude that adrenalectomy in the treatment of obliterating arteritis lacks all physiologic basis, as hyperepinephrinemia is not demonstrable in Buerger's disease nor can the removal of one adrenal gland have any physiologic effect. It is impossible to demonstrate general or lasting vasodilatation following such an operation. This statement is timely and necessary as, following the insistence of Oppel [241] and Leriche,[242] unilateral adrenalectomy has been performed in over 100 patients in Europe. Their careful analysis by Leibovici and Stricker [240] shows that the results are discouraging. It is interesting to note, however, that, according to White's recent work on the sensitization of sympathectomized vessels to epinephrine,[17] the circulating hormone is capable of producing spasm of the vessels, which can be experimentally abolished by adrenal denervation.[234]

Results of adrenal denervation in cases of vascular disease are unknown. Crile [243] states that the results do not as yet justify the application of this method in cases of Raynaud's disease.

239. Reid and Hermann.[74] Landis and Hitzrot.[175] de Takáts.[179]

240. Leibovici, R.: La surrénalectomie dans de traitement de l'artérite oblitérante, J. de chir. **44**:525 (Oct.) 1934. Stricker, P.: Bases physiologic indications, et résultats de la chirurgie des surrénales, ibid. **44**:513 (Oct.) 1934.

241. Oppel, W. A.: Die Raynaud'sche Krankheit als Hyperadrenalämia, Arch. f. klin. Chir. **149**:75, 1928.

242. Leriche, R., and Stricker, P.: Place de la surrénalectomie dans le traitement conservateur des artérites juvéniles, Presse méd. **40**:1237 (Aug. 10) 1932.

243. Crile, G.: Diseases Peculiar to Civilized Man, New York, The Macmillan Company, 1934.

EFFORTS TO ALLEVIATE PAIN

While it is well established that sympathetic neurons carry only efferent motor impulses, it has been amply demonstrated that "visceral pain" can be relieved by block of the sympathetic nerves. This is due in part to the presence of large myelinated fibers of the somatic type within the sympathetic trunk.[234] Evidence has also been brought forward [244] that sympathetic motor impulses liberate tissue metabolites which in turn stimulate the sensory nerve endings of somatic nerves. Moore and Singleton [245] have shown that pain originating from the arteries of the extremities traverses the somatic sensory nerves. In man, however, Foerster [246] especially has insisted on afferent sensory pathways in the vessels. It has also been suggested that the stimulation of sympathetic fibers changes the threshold of sensibility of the somatic nerves.[247]

Peripheral Nerve Block.—The injection of alcohol [248] and section and resuture [249] or crushing [234] of the peripheral nerves supplying the foot can be accomplished without motor paralysis, except that of the intrinsic muscles of the foot, which is unnoticed by the patient. The foot is completely desensitized, showing sensory and sympathetic paralysis, with the resulting vasodilatation and dryness. This vasodilatation is as great or almost as great as can be obtained by spinal anesthesia and may tide the patient over a critical and excruciatingly painful period. It does not relieve intermittent claudication. Its effect lasts from two to six months, at which time it can be repeated.

The incisions are made 6 inches above the ankle, and collateral circulation at this level must be adequate to insure primary healing. For complete desensitization of the foot, five nerves must be severed with meticulous technic. The drawback of the procedure is that an ascending infection, like a plantar abscess, may go unnoticed. Trophic ulceration, unless the nerves are completely severed, does not seem to occur.

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244. Davis, L., and Pollock, L. J.: The Rôle of the Sympathetic Nervous System in the Production of Pain in the Head, Arch. Neurol. & Psychiat. **27**:282 (Feb.) 1932.

245. Moore, R. M., and Singleton, A. O., Jr.: Studies on the Pain-Sensibility of Arteries: Peripheral Paths of Afferent Neurones from the Arteries of the Extremities and of the Abdominal Viscera, Am. J. Physiol. **104**:267, 1933.

246. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927.

247. Attenberger, H., and Kroll, F. W.: Ueber die vegetative Beeinflussung des somatischen Nervensystems, Arch. f. d. ges. Physiol. **223**:733, 1930.

248. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity: A Technique for Alcohol Injection of the Sensory Nerves of the Lower Leg, Surg., Gynec. & Obst. **51**:394, 1930.

249. Laskey, H. F., and Silbert, S.: Thrombo-Angiitis Obliterans: Relief of Pain by Peripheral Nerve Section, Ann. Surg. **98**:55, 1933.

This is a valuable procedure, especially adaptable to patients with Buerger's disease. In patients with diabetes or arteriosclerosis collateral circulation at the level of the incisions is often inadequate.

Paravertebral Block.—The use of this method to increase circulation and relieve pain in the extremities is relatively recent.[250] The technic is readily mastered by those familiar with this form of conduction anesthesia. When small amounts of concentrated procaine hydrochloride fail to produce the desirable effect on circulation and pain, 5 cc. of 95 per cent alcohol is injected into the necessary segments. This method is especially useful in instances of intractable pain in the lower extremities of older patients with arteriosclerosis without gangrene, to gain a temporary increase in circulation after ligation or embolism of a large artery, and in cases of Buerger's disease in which peripheral nerve block is not feasible. In the upper extremity, because of occasionally unavoidable intercostal neuritis, pleurisy and pneumothorax, the use of this method is more restricted. The complete interruption of sympathetic pathways is difficult at operation, and much less can be expected from dorsal paravertebral injections. For injections of procaine hydrochloride to relieve pain in cases of causalgia or neuroma of the stump and to test the value of sympathectomy, the method is most valuable.

Intraspinal Injection of Alcohol.—This method [251] has been tested recently in several clinics and should be reserved for cases of intractable pain of the extremity when simpler methods have failed. Aside from malignant processes, intractable neuroma of the stump [234] has been successfully treated. With careful technic complications have not been observed in a large number of cases.

Chordotomy.—Section of the spinothalmic tract for intractable pain in the extremities has seldom been carried out. The cases that have come to my knowledge or under my observation are not reported. Nevertheless, this possibility must be considered.

Amputations.—Technical improvements and mechanical considerations to improve the prosthetic value of the stump are outside the scope of this review. Extensive discussion of these problems can be found

250. Stern, E. L.: Alcohol Injection of Nerve Roots for Thrombo-Angiitis Obliterans, Am. J. Surg. **10**:107, 1930. Flothow, P. G.: Diagnostic and Therapeutic Injections of the Sympathetic Nerves, ibid. **14**:591, 1931. Reickert, F. L.: Intermittent Claudication Without Gangrene, Controlled by Sympathetic Nerve Block, Ann. Surg. **97**:503, 1933.

251. Dogliotti, A. M.: Traitement des syndromes douloureux de la périphérie par l'alcoolisation sub-arachnoïdienne des racines postérieures à leur émergence de la moelle épinière, Presse méd. **39**:1149, 1931.

in the new textbooks on surgery.[252] The indications, the proper time and the proper level of amputation in cases of peripheral vascular disease are of interest.

Amputation for intractable pain alone is hardly ever indicated since the advent of the special methods to relieve pain which have already been discussed. Amputation for restoring or improving function in a patient with a helpless, paralyzed part is an occasional consideration. But by far the most important indication for amputation is to remove a part which is hopelessly involved or which endangers the life of the patient because of absorption of toxins or spreading infection. With the advent of conservative methods which appeal to the patient and to the physician this last indication is often recognized too late and amputation is performed only as a hopeless gesture. Vascular disease still figures as the cause of about 30 per cent of all amputations in any large group of cases.[252] The incidence of amputations in cases of Buerger's disease is definitely decreasing with earlier diagnosis and adequate conservative treatment,[24] but even in Silbert's series the failure to avert a major amputation occurred in 9 per cent of his cases. Minor amputations, as the loss of digits, of course, are often necessary. If arterial thrombosis and embolism occur at unfavorable sites and if previously discussed conservative measures fail or are employed too late, amputation is required in a certain percentage of cases. The greatest percentage of amputations is performed in patients with arteriosclerotic or diabetic gangrene, those with the latter having an additional tendency to gangrenous infection and septicemia.

The determination of the peripheral vascular status and of the level of circulatory efficiency [253] is most important. The most useful tests to determine the proper level of amputation are the estimation of the skin temperature and the study of the cutaneous reaction to histamine. These two tests almost invariably indicate an identical level.

Worthy of emphasis is the fact that there is no one single factor, observation or test by which the optimal level of amputation can be determined.[254] The peripheral vascular status of the patient depends on age, the state of the cardiovascular apparatus and the immediate cause of the disease.

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252. Kirk, N. T.: Amputations, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 3, chap. 10. Wilson, P. D.: Amputations, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1932, vol. 3, p. 563.

253. de Takáts, G.: The Determination of the Proper Level of Amputation, Internat. J. Med. & Surg. **47**:339 (Sept.) 1934.

254. McNealy, R. W., and Shapiro, P. F.: Vascular Disease of the Lower Extremities: Review of Amputations; Criteria, Surg., Gynec. & Obst. **59**:650, 1934.

In cases of diabetic gangrene, which tax the surgeon's experience and skill to the highest degree, an important distinction has been made between the condition that is primarily due to deficient circulation and that which is primarily due to infection.[255] Naturally, both conditions may be present. While the former requires a major amputation, the latter is solved by minor amputation or sufficient drainage.

That education of the patient and close team-work between the physician and the surgeon are all-important is emphasized by Eliason.[256] Spinal anesthesia was used in 80 per cent and local anesthesia in 17 per cent of 170 operations for diabetic gangrene. The operative mortality was 3.5 per cent, the hospital mortality was 41.8 per cent, and the mortality within one year was 55 per cent. This material from the records of a large charity hospital naturally gives the highest percentages of failure. Half the patients with diabetic gangrene were unaware of the presence of diabetes.

The last report of McKittrick and Root [255] is more favorable. Again the importance of close team-work is obvious.

The growing tendency for conservatism in the treatment of peripheral vascular disease is obvious. But in the gangrenous state of older patients, especially in those with diabetes, conservatism must not lead to unnecessary delay in facing inevitable amputation. With accurate tests for collateral circulation the level and the optimal time of amputation may be determined on a safer basis than heretofore.

55 East Washington Street.

122 South Michigan Avenue.

255. McKittrick, L. F., and Pratt, T. C.: Principles of and Results After Amputation for Diabetic Gangrene, Ann. Surg. **100**:638, 1934.

256. Eliason, E. L.: Surgery of Diabetic Gangrene, Ann. Surg. **98**:1, 1933.

Book Reviews

Erbpathologie: Ein Lehrbuch für Aerzte. By O. Freiherr von Verschuer. Price, 8 marks; bound, 9 marks. Pp. 213, with 32 illustrations. Dresden: Theodore Steinkopff, 1934.

This book is the eighteenth volume of a series issued under the general title of "Medical Practice, a Collection of Special Subjects for the Improvement of Physicians." The idea is a good one, because each volume is written by a specialist well known in his particular line of work.

The pathology of heredity, or rather the pathologic conditions of the human body that can be transmitted by heredity, is perhaps no new problem even for those of the medical profession not versed in the complexities of mendelian transmission, but it is difficult for any one except the eugenist to really understand them. However, every one who has had even limited clinical experience cannot fail to be impressed by the occurrence of undesirable physical and psychic departures from the normal, that are frequently impossible to handle satisfactorily, among patients who apply for diagnosis and treatment. The menace to racial health of hereditary ailments, or the predisposition to such ailments can be thoroughly appreciated only after long years of tedious statistical investigation and the coordination of numerous individual investigations and public sources of information.

Frankly admitting the defects in the present knowledge, Verschuer discusses his subject in a masterly way, not devoting more space to the theory of the transmission of genes than is absolutely necessary for a grasp on the subject matter of the succeeding text. This theoretical consideration includes a discussion of mendelian heredity and its application to man, including the mechanism of recessive and dominant characteristics, mutation, the development and transmission of hereditary disease anlage and the effect of peristatic (environmental) influences on the individual.

The section on special pathology considers briefly about two hundred and fifty diseases, disease groups or predispositions which experience and observation have shown to be more or less dominant or recessive in transmission.

The final sections of the book are devoted to suggestions relative to the special training of physicians and students in the diagnosis of hereditary disease and the establishment of clinics for the rendering of expert opinion in difficult cases. Existing legal provisions make it obligatory that physicians work in conjunction with certain prescribed courts the duty of which is to decree sterilization, forbid marriage, allocate funds, etc., to those whom the state for one reason or another regards as liabilities to the public weal.

The statute relative to the prevention of hereditarily diseased progeny was promulgated on July 14, 1933. Too short a time has elapsed to enable one to draw any definite conclusions. Whether it will have a salutary effect on public health remains to be seen. Sterilization is the keynote and is seemingly being applied without fear or favor. It appears rational, when one is reminded that there are estimated to be 450,000 feebleminded, 280,000 persons with a schizophrenia and 20,000 or more afflicted with circular insanity within the Reich. All these ills fall within the category of dominant hereditary characteristics.

The burden of caring for this human wreckage is great for any country, and intelligent persons everywhere must ask themselves why these individuals should be allowed to propagate their kind unrestricted and to contribute their steadily increasing quota to the grand total of public enemies, delinquents and dependents. Doubtless Germany's experiment in Augean stable-cleaning will be watched with keen interest by all governments or organizations within the governments the interests of which center in the welfare of their people.

Verschuer's book, though somewhat difficult to understand by those not versed in the subject of heredity, contains much that can be read with considerable profit by all who think not so much in terms of the individual as of the stock.

Memoirs of a Small-Town Surgeon. By John B. Wheeler, M.D., Emeritus Professor of Surgery, University of Vermont College of Medicine. Price, $3. Pp. 336, with 4 illustrations. New York: Frederick A. Stokes Company, 1935.

To enjoy the full flavor of these memoirs one must be a physician with a drop of New England blood in his veins and preferably one who appreciates the Harvard Medical School and the Massachusetts General Hospital. For this is a book of reminiscences with a background vividly colored by Vermont, Harvard and the "M. G. H."

The tale begins with the autumn of 1875, when Wheeler entered the Harvard Medical School. Brave days they were: Oliver Wendell Holmes was teaching anatomy; young Henry P. Bowditch, physiology; Calvin Ellis, medicine, and Henry J. Bigelow, surgery. Fine days they were, too, for the lucky "House-pups" at the hospital, who on graduation from the School were taken in hand and "licked into shape" by such strong personalities as C. B. Porter, Bigelow himself or John Homans. All M. G. H. men the entire country over are the same: To them there is only one hospital, and this is The Hospital; tales of old days can never be retold too often—tales of Bigelow and his lithotrite, of Jack Elliot with his brilliant mind and winning personality, of the accident room and the flat.

The second part of the book deals with postgraduate education abroad when it was the traditional thing for American fledglings to make the grand tour in Europe for a year or so before settling down in practice. One is elected to honorary membership in that intimate little Viennese club of Bostonians who dined regularly during the early eighties on beer and conversation at the Riedhof and occasionally took to its bosom an outsider like Halsted of Baltimore; who worked hard all day under teachers like Billroth or Zuckerhandl; who enjoyed the opera or Strauss waltzes at night. Gay, happy, care-free days they were!

The third part of the book tells how a self-respecting, intelligent man of good training can succeed in the practice of medicine, always provided that he has imagination, a certain amount of humor in his make-up and the will to win. Wheeler settled down in Burlington, gradually built up his practice and did in his lifetime all the things a good physician would like to do: had medical adventures in country farmhouses and bitterly drawn-out battles against death, became professor of surgery in the University of Vermont, did his share of public health work, conquered an epidemic of diphtheria, kept abreast of the times and changed his way of doing things as new ideas and technics became established.

The volume as a whole is a fine tribute to the medical profession. All medical students will enjoy it. It is a good tonic, too, for tired physicians who in the long winter evenings occasionally wonder what is the use of trying to practice medicine well. Throughout this account of a particularly varied medical experience spanning many years one feels constantly the joy of conscientious, tireless endeavor for fine ideals.

Physiology in Modern Medicine. By J. J. R. Macleod. Seventh edition. Price, $8.50. Pp. 1154, with 297 illustrations. St. Louis: C. V. Mosby Company, 1935.

The seventh edition of this standard work in physiology appears after a lapse of five years. As this is a rather long interval from the time of the previous publication, there has necessarily been considerable revision of the text. One of the changes has been the removal of the word biochemistry from the title. Other new departures include the complete rewriting of certain chapters, a bibliography at the end of the volume instead of references at the end of each section and the addition of several new contributors.

Most of the sections have been written by Macleod. The rather long Part III has been extensively revised by E. P. Carter. The section on the endocrine organs has been revised by N. B. Taylor, and the section on the neuromuscular system, also quite long, has been rewritten by Philip Bard, whose name has not previously appeared in the list of co-authors. J. M. Peterson has revised the chapters on

the physicochemical basis of physiologic processes, and R. G. Pierce has assisted in the revision of Part II, devoted to the blood and lymph. J. M. Olmsted has written the section which has to do with special senses. It can be seen from this list of contributors and their contributions that the book is the composite presentation of several authors whose reputations in their special fields are as well established as is that of Macleod in his.

The book has been prepared with the express purpose of helping the clinician in applying physiology and biochemistry to medicine. This object has been kept in mind continuously by all the contributors, so that the book is not only an aid to the physiologist primarily and the student of physiology but also to the physician in the general field of medicine. The value of the book has been so well established that further comment hardly seems necessary. Unfortunately, the high standards of the contents of the book are negated in part by the extremely poor format. It seems a pity to spoil such a splendid scientific contribution by poor printing. Where changes have been made and new type has been used the result is a distinct difference in the degree of blackness, which makes for extremely difficult reading and spoils the appearance. The paper may be a poor type, because some of the illustrations taken from photographs are so indistinct and poorly reproduced that they would better have been omitted than incorporated.

Just at the time that this review was being prepared the death of Dr. Macleod was announced. It seems sad to think that this keen physiologist and brilliant scientist should have passed away at a comparatively young age. It is hoped that his book, however, will not die but will be continued by his co-authors and others who are interested in physiology, and that future editions will appear from time to time.

The Nervous Patient. By Charles P. Emerson, Research Professor of Medicine, Indiana University. Price, $4. Pp. 453. Philadelphia: J. B. Lippincott Company, 1935.

New efforts in medicine always are interesting. Emerson has attempted something new in that as an internist he has put together a book which deals largely with the functional manifestations of disease and in so doing has invaded a field usually claimed by the neurologist or psychiatrist and rarely trespassed on by others. He has written his book with a definite purpose in mind: General practitioners are the ones in the profession of medicine who see organic and mental diseases in early stages when perhaps prevention or cure is possible, and he has dedicated the work to them, hoping evidently to arouse their interest in an important aspect of preventive medicine.

The book has a great deal of character and individuality. In parts it is much like a short textbook of general medicine with chapters on heart disease, pulmonary disease, genito-urinary disease and gastro-intestinal disease. These chapters are written, however, with especial emphasis on the various functional abnormalities which are likely to complicate the clinical picture of any chronic organic disturbance.

About half the book deals with "nervousness": disorders of sleep and of personality, the psychoneuroses and hysteria and, finally, the more serious "nervous" disorders, such as the manic-depressive psychoses and dementia praecox. The writing is simple and easy to follow; the printing is good, and the general appearance of the book agreeable to the eye and hand. On the whole, it can be recommended. Practitioners and students can learn a great deal from it.

Diabetes Mellitus and Obesity. By Garfield G. Duncan. Price, $2.75. Pp. 227, with 40 tables. Philadelphia: Lea & Febiger, 1935.

Although insulin has been available for nearly fifteen years, most diabetic patients are still handled by the old Naunyn method of restricting carbohydrate. If insulin is prescribed, it is usually in a haphazard and inaccurate way, and the patient rarely eats a carefully weighed and measured diet. The cause of this unsatisfactory state of affairs is, the reviewer believes, evident: It is simple to

grasp the theoretical requirements of diet (and of insulin), but when it comes to translating a food formula into actual meals the ordinary physician fails miserably; he is, in fact, unable to do it. Hence unless he sees enough patients with diabetes to justify a special setup, including a dietitian-teacher for his patients, he follows the line of least resistance, which is to tell them not to eat sugar and starch and to give insulin in a vague and half-hearted way. Furthermore, the racketeers in the field of diabetes have written so much—each exploiting his own system of management—that most physicians are terrified into inferiority and withdraw behind the protection of inertia.

To remedy all this a great many small books have been written on diabetes, designed to make the treatment so simple for both patient and physician that any one can carry it out. The reviewer questions whether so far they have solved the problem.

In the present instance the reviewer has only praise to bestow. Duncan's book is clear, precise and sound and is stripped of complicated extraneous matter. It is a most useful work for the general practitioner to have on his table for quick reference in emergencies and to refresh his mind on diabetic problems.

Methods of Treatment. By Logan Clendening, M.D., Clinical Professor of Medicine in the Medical Department of the University of Kansas. Fifth Edition. Price, $10. Pp. 879, with 102 illustrations. St. Louis: C. V. Mosby Company, 1934.

This is an interesting book with a colorful personality. When it made its début in 1924 its aim was to furnish physicians an outline of all the methods of treatment in internal medicine. Less was known then than now, so that the book was shorter and rather less profusely illustrated than at present, but otherwise it was of about the same general character. It created at once an enviable reputation. Each subsequent edition has been warmly welcomed, so that doubtlessly what was said of the fourth edition was no exaggeration (ARCH. INT. MED. **47**:988 [June] 1931): "This book still remains the classic in the field of medical treatment for the practitioner and student. The lucid manner in which it is written and the fact that it includes every important field in medical therapeutics make it a necessary addition to any medical library."

The fifth edition keeps the volume fully up to the standard of its elders. Clendening states that the revision is the most thorough that has been made since the book was first set up. It appears to be very complete. Certainly this book continues to be delightfully written and has the proper appurtenances that a successful book should have in the way of good paper, clear printing and easily understandable diagrams. It will continue to be a highly respected and useful member of all self-respecting medical libraries.

Diseases of Children, with Contributions by 36 Authors. Edited by Hugh Thursfield and Donald Paterson. Third edition. Price, $10. Pp. 1152, with 277 illustrations. Baltimore: William Wood & Company, 1934.

This is an English book distributed in this country. Nicely printed and profusely illustrated, it is a cooperative effort in the field of pediatrics similar to those of Cecil, Musser and Conybeare in general medicine. The result is an excellent miniature encyclopedia of pediatrics, but, as in all of these group compilations, one misses the personality and point of view of a single outstanding master. A vast field is covered, and there is of course considerable duplication of what is adequately discussed in textbooks of internal medicine. Hence, some of the articles on important topics are too brief to be of great value, and at times too much space is given to rare and curious conditions. On the whole, the book seems adequate, but it does not rouse one's enthusiasm.